Drug Class Review
on
Nasal Corticosteroids

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The Agency for Healthcare Research and Quality has not yet seen or approved this report

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Dana Selover, MD
Colleen Smith, PharmD
Kim Peterson, MS

Oregon Evidence-based Practice Center
Oregon Health & Science University
Mark Helfand, MD, MPH, EPC Director
Terri Bianco, PharmD, Project Director

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INTRODUCTION

Allergic rhinitis is a condition characterized by sneezing, watery rhinorrhea, nasal itching, congestion, itchy palate, and itchy, red, and watery eyes.[1] The prevalence of allergic rhinitis has increased significantly over the last 15 years and the disease currently affects twenty to forty million Americans.[2] It is estimated that in 2002, approximately 14 million medical office visits were attributed to allergic rhinitis.[2] Many suffering from allergic rhinitis are children and young adults, when, if treated early, may to avoid later stage complications.[3] If left untreated, this condition may lead to the development or worsening of co-morbidities including: chronic or recurrent sinusitis, asthma, otitis media, or respiratory infections.[4, 5] Moderate to severe allergic rhinitis may also lead to sleep disorders, fatigue and learning problems.[3, 5]

Rhinitis can be divided into two broad categories: allergic and non-allergic. Allergic rhinitis consists of seasonal and perennial rhinitis. Seasonal allergic rhinitis, also called hay fever, is characterized by symptoms that occur in response to specific seasonally occurring allergens. Allergens may include pollen from trees, grasses, and weeds. Perennial allergic rhinitis occurs throughout the year and is caused by allergens such as house dust mites, animal dander, cockroaches and molds. In some geographic locations pollen can play a role in perennial rhinitis. Patients are often sensitized to both seasonal and perennial allergens, which can be termed, mixed allergic rhinitis.[6]

There is a prominent genetic component involved in the development of allergic rhinitis. Individuals with both parents suffering from atopic disease have 50% or greater chance of affliction with allergic disease.[5] The symptoms of allergic rhinitis are caused by an IgE-mediated immune response to a particular allergen. An antibody, called immunoglobulin E (IgE), represents a major component of this immunogenic reaction. The binding of the allergen to IgE molecules leads to a chain of events, which includes the release of mediators such as histamine and leukotrienes, and culminates in the arrival of inflammatory cells to the region. These inflammatory cells are responsible for the clinical symptoms of allergic rhinitis.

In contrast, non-allergic rhinitis is often a diagnosis of exclusion and represents a diverse group of disorders. There are several different types of non-allergic rhinitis: drug induced, gustatory, hormonal, infectious, non-allergic rhinitis with eosinophilia syndrome, occupational, anatomic, and vasomotor.[7] A classification according to the presence or absence of inflammatory cells in nasal scrapings has also been suggested in order to find the most effective treatment.[8] The symptoms of non-allergic rhinitis are similar to allergic rhinitis and include: nasal obstruction, rhinorrhea, and congestion. Nasal itch and conjuctival irritation may be less with non-allergic versus allergic rhinitis.[5]

There are several types of treatments available for allergic and non-allergic rhinitis. Allergen avoidance isn't always possible for patients with allergic rhinitis. These patients can use oral or nasal antihistamines and decongestants without a prescription. Nasal mast cell stabilizers, oral leukotriene modifiers, anticholinergic nasal spray, systemic and nasal corticosteroids, anti-IgE monoclonal antibodies and immunotherapy can be obtained with a prescription from a healthcare provider. Treatment for non-allergic rhinitis focuses on symptom management and includes several of the aforementioned medications.

Nasal corticosteroids are a safe and effective treatment option for both allergic and non-allergic rhinitis. There are currently 6 different nasal corticosteroid preparations

on the U.S. market (*Table 1*.) The nasal sprays differ with respect to delivery device and propellant, as well as potency and dosing frequency. When used daily, nasal corticosteroids significantly reduce nasal congestion, sneezing, rhinorrhea, and other symptoms.[6]

Overall, the nasal preparations are well tolerated and patients experience few, if any, adverse effects. These include nasal irritation, nasal dryness, mild to moderate epistaxis, transient headache and dizziness (should we add a few more like, local fungal infections, cataract etc.). In treating children there are the additional concerns about more serious adverse events such as potential growth inhibition, hypothalamic-pituitary-adrenal suppression and ophthalmologic adverse effects.

Table 1. Nasal Corticosteroid Indications and Recommended Doses

Generic Name	Trade Name	Nasal Polyps	Nonallergic (Vasomotor) Rhinitis	Perennial AR	Seasonal AR	Dosage in Adults	Dosage in Children
Beclomethasone	Beconase AQ ® (42 mcg/spray)	**X**	**X**	**X**	**X**	1-2 spray EN 2x/day Maximum dose: 2 sprays EN 2x/day	(6-12 years old): 1 spray EN 2x/day Maximum dose: 2 sprays EN 2x/day
Budesonide	Rhinocort Aqua®[a] (32 mcg/spray)			**X**	**X**	1 spray EN daily Maximum dose: 4 sprays EN once daily	(≥ 6 years old): 1 spray EN once daily Maximum dose (<12 years old): 2 sprays EN once daily
Flunisolide*	Generic flunisolide (25 mcg/spray) Nasarel® (29 mcg/spray)			**X**	**X**	2 sprays EN 2x/day. May increase dose to 2 sprays EN 3x/day Maximum dose: 8 sprays EN once daily	(6-14 years old): 1 spray EN 3x/day or 2 sprays EN 2x/day Maximum dose: 4 sprays EN once daily
Fluticasone	Generic fluticasone (50 mcg/spray) Flonase® (50 mcg/spray)		**X**	**X**	**X**	2 sprays EN once daily Or 1 spray EN 2x/day \ Maximum dose: 2 sprays EN once daily	(≥4 years old): 1 spray EN once daily Maximum dose: 2 sprays EN once daily
Mometasone	Nasonex® (50 mcg/spray)	**X (≥18 years old)**		**X**	**X**[c]	2 sprays EN once daily Nasal polyps: 2 sprays EN twice daily	(2-11 years old): 1 spray EN once daily
Triamcinolone	Nasacort AQ® (55 mcg/spray) Nasacort HFA®[b] (55 mcg/spray)			**X**	**X**	Nasacort AQ® and HFA®: 2 sprays EN once daily Nasacort HFA®: May increase to 4 sprays EN once daily Maximum dose: Nasacort AQ®: 2 sprays EN once daily Nasacort HFA®: 4 sprays EN once daily	(6-11 years old): Nasacort AQ®: 1 spray EN once daily Nasacort HFA®: 2 sprays EN once daily Maximum dose: Nasacort AQ® and HFA®: 2 sprays EN once daily

[a] FDA pregnancy category B, all others category C.

[b] Metered-dose aerosol spray, all others are metered-dose pump sprays with or without nasal adaptors. Manufacturer expects product to be available for purchase at the end of the 1st quarter 2006.
c Treatment and prophylaxis: Prophylaxis of seasonal allergic rhinitis with mometasone (200 mcg/day) is recommended 2-4 weeks prior to anticipated start of pollen season.
* Flunisolide was originally marketed as Nasalide® but was reformulated with a decrease in propylene glycol content in the vehicle. The new product, Nasarel® was approved by the FDA in March 1995. Nasalide® is no longer available for purchase on the US market; however, at the time of this paper there was a generic for Nasalide® manufactured by Bausch and Lomb.
EN= each nostril
AR= allergic rhinitis

Scope and Key Questions

The purpose of this review is to help policymakers and clinicians make informed choices about the use of nasal corticosteroids. Our goal is to summarize comparative data on efficacy, effectiveness, tolerability, and safety.

Report authors drafted preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by the Washington State Preferred Drug Program (PDP), the collaboration that commissioned this review (Health Care Authority (HCA), the Department of Social & Health Services (DSHS) and the Department of Labor & Industries (L&I). Washington State PDP is responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. Washington State PDP approved the following key questions to guide this review:

1. For adults and children with seasonal or perennial (allergic and non-allergic) rhinitis, do nasal corticosteroids differ in effectiveness?

2. For adults and children with seasonal or perennial (allergic and non-allergic) rhinitis, do nasal corticosteroids differ in safety or adverse events?

3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities, or in pregnancy and lactation for which one nasal corticosteroid is more effective or associated with fewer adverse events?

Inclusion Criteria

Population(s):

Adult patients and children (under age 18) in outpatient settings with the following diagnosis:

- Seasonal allergic rhinitis
- Perennial allergic rhinitis
- Non-allergic rhinitis

Table 2. Interventions

Generic Name	Trade Name	Forms
Mometasone	Nasonex	Nasal spray
Fluticasone	Flonase	Nasal spray
Budesonide	Rhinocort, Rhinocort Aqua	Nasal spray
Triamcinolone	Nasacort, Nasacort AQ	Nasal spray
Beclomethasone	Beconase, Beconase AQ, Vancenase, Vancenase AQ	Nasal spray
Flunisolide	Nasalide, Nasarel	Nasal spray

Effectiveness outcomes

1. Symptomatic relief
2. Onset of action

Safety outcomes

- Overall adverse effect reports
- Withdrawals due to adverse effects
- Serious adverse events reported
- Specific adverse events (localized infection of nasal mucosa, hypersensitivity, hypercorticism, HPA suppression, growth suppression in pediatric population, headache, throat soreness, dry mouth, nasal irritation)

Study designs

1. For effectiveness, controlled clinical trials and good-quality systematic reviews.
2. For safety, in addition to controlled clinical trials, observational studies will be included.

METHODS

Literature Search

To identify relevant citations, we searched the Cochrane Central Register of Controlled Trials (4th Quarter 2005) and MEDLINE (1966 to October Week 3 2005) using terms for included drugs, indications, and study designs (see Appendix A for complete search strategies). To identify additional studies, we also searched reference lists of included studies and reviews, FDA information (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/), and dossiers submitted by pharmaceutical companies. All citations were imported into an electronic database (EndNote 9.0).

Study Selection

Reviewers (C.S. and K.P.) assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above. Full-text articles of potentially relevant abstracts were retrieved and a second review for inclusion was conducted by reapplying the inclusion criteria.

Data Abstraction

The following data were abstracted from included trials: study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment, and results for each outcome. We recorded intention-to-treat results when reported. In cases where only per-protocol results were reported, we calculated intention-to-treat results if the data for these calculations were available. In trials with crossover, outcomes for the first intervention were recorded if available. This was because of the potential for differential withdrawal prior to crossover biasing subsequent results and the possibility of either a "carryover effect" (from the first treatment) in studies without a washout period, or "rebound" effect from withdrawal of the first intervention.

Data abstracted from observational studies included design, eligibility criteria duration, interventions, concomitant medication, assessment techniques, age, gender, ethnicity, number of patients screened, eligible, enrolled, withdrawn, or lost to follow-up, number analyzed, and results.

Quality Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix B. These criteria are based on the U.S. Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (U.K.) criteria.[9, 10] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw in one or more categories were rated "poor-quality"; trials that met all criteria were rated "good-quality"; the remainder were rated "fair-quality." A fatal flaw occurs when there is evidence of bias or confounding in the trial, for example when randomization and concealment of allocation of random order are not reported and baseline characteristics differ significantly between the groups. In this case, randomization has apparently failed and for one reason or another bias has been introduced.

As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. Those studies considered only *probably* valid are indicated as such using a "fair-poor" rating. A poor-quality trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. External validity of trials was assessed based on whether the publication adequately described the study population, how similar patients were to the target population in whom the intervention will be applied, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the role of the funding source.

Appendix B also shows the criteria we used to rate observational studies. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good-quality for adverse event

assessment if they adequately met six or more of the seven predefined criteria, fair-quality if they met three to five criteria and poor-quality if they met two or fewer criteria.

Included systematic reviews were also rated for quality based on pre-defined criteria (see Appendix B), based on a clear statement of the questions(s), inclusion criteria, adequacy of search strategy, validity assessment and adequacy of detail provided for included studies, and appropriateness of the methods of synthesis.

Overall quality ratings for the individual study were based on internal and external validity ratings for that trial. A particular randomized trial might receive two different ratings: one for effectiveness and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

Evidence Synthesis

Effectiveness versus Efficacy. Throughout this report, we highlight *effectiveness* studies conducted in primary care or office-based settings that use less stringent eligibility criteria, assess health outcomes, and have longer follow-up periods than most *efficacy* studies. The results of effectiveness studies are more applicable to the "average" patient than results from highly selected populations in efficacy studies. Examples of "effectiveness" outcomes include quality of life, global measures of academic success, and the ability to work or function in social activities. These outcomes are more important to patients, family and care providers than surrogate or intermediate measures such as scores based on psychometric scales.

An evidence report pays particular attention to the generalizability of *efficacy* studies performed in controlled or academic settings. *Efficacy* studies provide the best information about how a drug performs in a controlled setting that allow for better control over potential confounding factors and bias. However, the results of efficacy studies are not always applicable to many, or to most, patients seen in everyday practice. This is because most efficacy studies use strict eligibility criteria which may exclude patients based on their age, sex, medication compliance, or severity of illness. For many drug classes severely impaired patients are often excluded from trials. Often, efficacy studies also exclude patients who have "comorbid" diseases, meaning diseases other than the one under study. Efficacy studies may also use dosing regimens and follow up protocols that may be impractical in other practice settings. They often restrict options, such as combining therapies or switching drugs that are of value in actual practice. They often examine the short-term effects of drugs that, in practice, are used for much longer periods of time. Finally, they tend to use objective measures of effect that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

Data Presentation. We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. Studies that evaluated one nasal corticosteroid against another provided direct evidence of comparative benefits and harms. Outcomes of changes in symptom measured using scales or tools with good validity and reliability are preferred over scales or tools with low validity/reliability or no reports of validity/reliability testing. Where possible, head-to-head data are the primary focus of the synthesis. No meta-analyses were conducted in this review due to

heterogeneity in treatment regimens, use of concomitant medications, outcome reporting and patient populations.

In theory, trials that compare these drugs to other interventions or placebos can also provide evidence about effectiveness. This is known as an indirect comparison and can be difficult to interpret for a number of reasons, primarily issues of heterogeneity between trial populations, interventions, and assessment of outcomes. Indirect data are used to support direct comparisons, where they exist, and are also used as the primary comparison where no direct comparisons exist. Such indirect comparisons should be interpreted with caution.

RESULTS

Overall results of literature search

We identified 1,404 articles from literature searches and reviews of reference lists. This includes citations from dossiers submitted by the manufacturers of mometasone, fluticasone and budesonide. After applying the eligibility and exclusion criteria to the titles and abstracts, we obtained copies of 489 full-text articles. After re-applying the criteria for inclusion, we ultimately included 84 publications. The results of our literature search are detailed in Appendix C.

Overall summary of the evidence

- No effectiveness trials were identified

- **SAR in adults**: All nasal corticosteroids had similar effects on rhinitis symptoms overall and resulted in significant improvement in up to 78% to 88% of adults with SAR in head-to-head trials

- **PAR in adults:** Very few differences in efficacy were reported in head-to-head trials involving beclomethasone, budesonide, fluticasone, mometasone in adults with PAR. Outcome reporting was heterogenous was insufficient for quantifying effects across trials

    - Budesonide aqueous 256 mcg was associated with a significantly greater mean point reduction in a combined nasal symptom score relative to fluticasone aqueous 200 mcg (-2.11 vs -1.65, p=0.031) in one 6-week trial of 273 patients[11]
    - Unknown how new form of flunisolide or triamcinolone compare to other nasal corticosteroids due to a lack of head-to-head trial evidence

- Quality of life outcomes were rarely reported in head-to-head trials and beclomethasone, fluticasone and triamcinolone were associated with similar levels of improvement

- Overall, rates of withdrawals due to adverse events, headache, throat soreness, epistaxis and nasal irritation were generally similar between nasal corticosteroids in head-to-head trials of equivalent dosages of drugs in adults with SAR or PAR. One exception was that the old form of flunisolide was associated with significantly higher rates of nasal burning/stinging than beclomethasone AQ and the newer form of flunisolide across two head-to-head trials of adults with SAR.

- Cataract development was reported in only observational study and results suggest that beclomethasone was not associated with any increased risk relative to non-use

- No trials or observational studies were identified that assessment risk of worsening glaucoma.

- Mometasone is the only NCS with prophylactic use as a labeled indication. Mometasone was associated with lower levels of rhinitis symptom severity during pre- and peak-seasons relative to beclomethasone; but, this may have been at the expense of increased risk of headache with mometasone

- No head-to-head trials of adults with non-allergic rhinitis were identified

- In children, head-to-head trials of SAR and PAR are few and beclomethasone, fluticasone, and mometasone were associated with similar reductions in rhinitis symptoms and with similar rates of more common respiratory and nervous system adverse effects. Evidence from placebo-controlled trials was insufficient for further assessment of comparative effects.

- Growth retardation in children:

    - Beclomethasone associated with significantly lower height increase over 12 months relative to placebo in one trial and similar to expected height increases over 3 years in a retrospective observational study
    - **Fluticasone and mometasone each associated with s**imilar height increases over 12 months relative to placebo

- Budesonide was associated with development of 2 cases of transient lenticular opacities in an uncontrolled retrospective study of 78 children over a 2-year period; the clinical significance of the opacities was not reported

- No trials of children with non-allergic rhinitis were identified.

- Limited evidence is insufficient to draw any conclusions about comparative effectiveness, efficacy or safety can be for subgroups based on demographics, concomitant use of other medications, comorbidities (e.g., asthma, daytime somnolence/sleep disturbances) or pregnancy rhinitis

Detailed assessment

Key Question 1.
For adults and children with seasonal or perennial (allergic and non-allergic) rhinitis, do nasal corticosteroids differ in effectiveness?

Seasonal Allergic Rhinitis (SAR)

I. Adults with SAR

A. Results of literature search for trials in adults with SAR

We included 15 head-to-head trials of nasal corticosteroids for the treatment of SAR (Evidence Tables 1 and 2).[12-26] Three studies compared beclomethasone versus flunisolide[12, 19, 25], two beclomethasone versus mometasone,[24, 27] two flunisolide (Nasarel) versus flunisolide (Nasalide),[16, 23]two triamcinolone aqueous vs fluticasone,[22, 26] two beclomethasone versus fluticasone,[15, 20] one triamcinolone aerosol versus fluticasone,[14] one budesonide versus fluticasone,[13] one beclomethasone versus triamcinolone aqueous,[18]and one beclomethasone versus budesonide (Table 3).[17]

Table 3. Head-to-head trial comparisons in adults with SAR

	BDP	*FN*	*TAA*	*FP*	*MF*	BUD
BDP		**3**	**1**	**2**	**2**	**1**
FN		**2[a]**				
TAA				**3[b]**		
FP						**1**
MF						
BUD						

Abbreviations: BDP=beclomethasone dipropionate, FN=flunisolide, TAA=triamcinolone acetonide, FP=fluticasone propionate, MF=mometasone furoate, BUD=budesonide

[a] *Flunisolide (Nasalide) was reformulated to flunisolide (Nasarel) and two head-to-head trials were conducted.*

[b] *One trial used triamcinolone aerosol nasal spray propelled with CFC; however, the only product currently available in the US is propelled with HFA*

B. Description of trials of adults with SAR

The studies ranged from 2 to 8 weeks in duration and there were no open-label studies. There were two studies which had both single-blind and double-blind treatment arms,[12, 13] seven studies were single blind, [14, 17-19, 22, 25, 26] five studies were double-blind,[15, 16, 20, 23, 24] one trial was double-dummy,[27] and one study had a cross-over design.[23] The cross-over study was designed primarily to examine the adverse effects between two medications and thus efficacy was only a secondary measure.[23] The double-dummy design presents some unique issues for study interpretation with this particular class of medications. The patients in this type of trial were exposed to the active drug and the placebo vehicle of the comparator. This creates some uncertainty for interpretation of the adverse events as sometimes it is the vehicle and not the active ingredient that is

responsible for certain adverse effects. In addition, this study design requires the patient to use multiple sprays of nasal product into the nose (in this case 16 sprays per day) which can possibly irritate the nasal mucosa as well as potentially dilute or displace the active medication if the placebo is sprayed into the nostril directly afterward.

Trial populations were heterogenous in terms of demographic characteristics (Table 4). Only 40 percent of trials characterized trial populations by race and in those, the majority of patients were white (81.3-99%).[13, 18, 22, 24-26] Gender was reported in all but one trial,[23] and proportions of female patients ranged widely; from 8.5%[28] to 66.7%.[19] Mean age ranged from 24 years[20] to 66.7 years.[19] Baseline illness severity assessment methods also differed across trials and this is another potential source of heterogeneity across patient populations. Trials also differed in which, if any, concomitant treatments were allowed and whether use of these was recorded.

Table 4. SAR trial characteristics

Trial	Mean age (yrs)	% female	% white	Quantitative baseline nasal symptom requirement	24-month SAR symptom history required	Skin prick test required	Concomitant antihistamine use allowed?	Concomitant immunotherapy allowed?
Kaiser 2004	31.6	62	81.7	42/84 (TNSS)	√	√		
Gross 2002	38.8	66.5	81.3	42/84 (TNSS)	√	√		√
Ratner 1992	37.1	45.3	NR	200/400 (INSS)	√	√	√	
Graft 1996*	34.7	47	93	TNSS ≤ 2	√	√		√
McArthur 1994	27	51	NR				√	
Langrick 1984	66.7	37.5	NR					√
Ratner 1996	44	62	NR	TSS = 2-7	√	√	√	√
Welsh 1987	28	33	NR		√	√	√	√
Stern 1997	NR	44	99		√	√	√	
Greenbaum 1988	NR	NR	NR		√	√	√	
Hebert 1996	32	8.5	NR	TSS ≥ 6; congestion ≥ 2 + one other symptom (INSS)	√	√	√	√
Lumry 2003	37	51	86.5	≥ 24 of 48 (RIS)	√	√	√	√

Trial	Mean age (yrs)	% female	% white	Quantitative baseline nasal symptom requirement	24-month SAR symptom history required	Skin prick test required	Concomitant antihistamine use allowed?	Concomitant immunotherapy allowed?
Small 1997	28	52	NR	≥ 24 of 48 (RIS)	√	√		√
LaForce 1994	24	29	NR	200/400 (INSS)		√		√
Bronsky 1987	29	52	91	≥ 8 (EENT)	√	√		

*Prophylaxis trial; TNSS=Total Nasal Symptom Score; Individual Nasal Symptom Score; Total Symptom Score; Rhinitis Index Score; Eye, Ear, Nose & Throat

No SAR trial was rated good quality. All but one trial was rated fair quality.[23] The only trial rated poor suffered from multiple flaws including inadequately described randomization and allocation concealment methods, a complete lack of inclusion criteria and reporting of baseline demographics, and excluded a number of patients from the outcome assessment.[23] The majority of the trials were sponsored by the pharmaceutical industry. Sponsor information was not reported in one trial[19] and three trials[23, 25, 28] did not acknowledge receiving funding but had authors employed by pharmaceutical companies.

C. Results of trials of treatment of adults with SAR

1. Direct comparisons

Similar proportions of patients experienced significant global improvements in rhinitis symptoms after 3 to 7 weeks of treatment based on physician ratings in head-to-head trials of nasal corticosteroids (Table 5). The ranges of improvement rates are as follows: 34% to 87% of patients taking beclomethasone 168 to 400 mcg,[12, 15, 17-20, 25, 28] 27% to 80% of patients taking flunisolide 200 or 300 mcg,[12, 19, 25] 53% to 82% of patients taking fluticasone 200 mcg,[13-15, 20-22] 78.4% of patients taking triamcinolone AQ 200 mcg,[18] 77% to 79% of patients taking mometasone 100 or 200 mcg,[28] and 88% of patients taking budesonide 128 or 256 mcg.[13] Global improvement was the most commonly reported outcome, was defined differently across trials, and was generally rated based on patient diary ratings (0=none; 3=severe) of nasal symptom severity of rhinorrhea, stuffiness/congestion, nasal itching, and sneezing.

Potential factors were identified that were possibly associated with the noticeably lower patient improvement rates observed in three trials. The lowest rates of patient improvement were observed in a 7-week trial of flunisolide 200 mcg versus beclomethasone 400 mcg (29% vs 34%, NS).[19] Reasons for why the rates in this trial differed from the others may have been that the mean age was noticeably higher at 66.7 years and the outcome definition of "total improvement" appeared to be more stringent than in the other trials. Rates of patient improvement were also quite low in a 4-week trial of flunisolide 200 or 300 mcg versus beclomethasone 168 or 336 mcg (27% vs 38% vs 40% vs 46%; NS). That was unique, in that it was the only trial to prohibit

concomitant usage of both antihistamines and immunotherapy.[25] The only unique characteristic of the trial of fluticasone 200 mcg versus beclomethasone 336 mcg that had the third lowest patient improvement rates (53% vs 59%, NS) was that it had the shortest treatment period of only two weeks and the treatments may not have reached their maximum effect within that time.[15]

Only three trials pre-specified primary outcome measures. Mean change in composite rhinitis symptom score was chosen for all three of these trials.[13, 14] Measurement of change in composite symptom scores was also the second most commonly reported outcome; however, these were defined differently across trials.(Table 5) There were no significant differences between any two nasal corticosteroids in any of the trials that reported these outcomes for the treatment periods overall.[12-14, 16, 18, 20-22, 28] There was a difference in one trial when symptom scores were analyzed only on days when the pollen count was greater than 10 grains/m^3.[13] Results of this trial demonstrated that budesonide 256 mcg per day was significantly more effective in reducing combined symptom scores, as well as, the individual scores for sneezing and runny nose when compared to fluticasone and budesonide 128 mcg daily.[13]

Of note are the efficacy findings from the Greenbaum 1998 trial that are not reflected in Table 5, which pertain to the comparison of the new and old formulations of flunisolide.[23] The focus of this trial was on comparative tolerability. The original formulation of flunisolide uses a vehicle containing a mixture of polyethylene glycol and propylene glycol. The product was re-formulated due to a relatively high incidence of transient local burning and stinging. The new formulation of flunisolide contains a reduced amount of propylene glycol, five percent as compared to twenty percent found in the original formulation.[23] Both products are still available in the US market. This trial did report a few efficacy outcomes, however, and findings indicated that approximately 54% of patients reported no differences between the new and old forms of flunisolide in controlling nasal symptoms overall. This finding is consistent with the finding of the other 6-week trial of the new and old formulations of flunisolide that both were associated with similar mean total symptom scores on peak pollen days (3.81 vs 3.55, NS).[16]

Table 5. Rhinitis symptom assessment outcomes in adults with SAR

Study Sample size Trial duration	Age % female	Treatment A	Treatment B	Physician-rated global evaluation of improvement (% pts)	% Change in total symptom score
McArthur 1994 n=77 3 wks	27 yrs 51%	Budesonide 200 mcg	Beclomethasone 200 mcg	Noticeably, very or total effective: 85% vs 82%, NS	NR
Langrick 1984 n=60 7 wks	66.7 yrs 37.5%	Flunisolide 200 mcg	Beclomethasone 400 mcg	Total improvement: 29% vs 34%, NS	NR
Welsh 1987 n=100 6 wks	28 yrs 33%	Flunisolide 200 mcg	Beclomethasone 336 mcg	Substantial (patient-rated): 80% vs 75%, NS	Total hay fever score: +13.1% vs +96.4%, NS

Study Sample size Trial duration	Age % female	Treatment A	Treatment B	Physician-rated global evaluation of improvement (% pts)	% Change in total symptom score
Bronsky 1987 n=151 4 wks	29 yrs 52%	Flunisolide 200 or 300 mcg	Beclomethasone 168 OR 336 mcg	Major improvement: 27% vs 38% vs 40% vs 46%, NS	NR
Ratner 1992 n=136 2 wks	44 yrs 62%	Fluticasone 200 mcg	Beclomethasone 336 mcg	Significant or moderate: 53% vs 59%, NS	NR
Laforce 1994 n=238 4 wks	24 yrs 29%	Fluticasone 200 mg BID or QD	Beclomethasone 336 mcg	Significant or moderate: 65% vs 70% vs 65%, NS	TNSS: -43% vs -53% vs -32%, NS
Hebert 1996 n=477 4 wks	32 yrs 8.5%	Mometasone 100 or 200 mcg	Beclomethasone 400 mcg	Complete/marked relief: 77% vs 79% vs 74%, NS	Primary outcome of mean change in TNSS NR due to inadequate data
Lumry 2003 n=147 3 wks	37 yrs 51%	Triamcinolone AQ 220 mcg	Beclomethasone 336 mcg	Greatly or somewhat improved: 78.4% vs 87%, NS	Nasal Index: -42.9% vs -45.9%, NS
Stern 1997 n=635 4-6 wks	Age NR 51%	Budesonide 128 or 256 mcg	Fluticasone 200 mcg	Substantial or total control - patients: 85% vs 88% vs 82%, NS	Combined nasal symptom score**: -26.5% vs -29.4% vs -29.4%, NS
Kaiser 2004 3 wks	31.6 yrs 62%	Triamcinolone AQ 220 mcg vs	Fluticasone 200 mcg	NR	TNSS: -48% vs -49.7%, NS
Gross 2002 n=352 3 wks	38.8 yrs 66.5%	Triamcinolone AQ 220 mcg vs	Fluticasone 200 mcg	NR	TNSS: -49.4% vs -52.7%, NS
Small 1997 n=233 3 wks	28 yrs 52%	Triamcinolone HFA 220 mcg vs	Fluticasone 200 mcg	NR	RIS**: -55% vs -60%, NS
Ratner 1996 n=218 6 wks	44 yrs 62%	New flunisolide 200 mcg	Old flunisolide 200 mcg	NR	TNSS means: 3.81 vs 3.55; NS
Greenbaum 1988 n=122 4 wks	NR NR	New flunisolide 200 mcg	Old flunisolide 200 mcg	NR	NR

Three trials reported quality of life outcomes based on assessments using the 28-item Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).[18, 22, 26] RQLQ items are organized into seven dimensions (activities, emotions, eye symptoms, nasal symptoms, non-hay fever problems, practical problems and sleep) and each are rated using a 7-point Likert Scale (0 to 6; lower scores indicate better QOL). Triamcinolone AQ 220 mcg was associated with similar mean reductions in RQLQ total score after 3 weeks relative to beclomethasone[18] and fluticasone (Table 6).[22, 26]

Table 6. Mean change in RQLQ Total Score

Study Sample size Trial duration	Age % female	Treatments	Point reductions
Lumry 2003 n=147 3 wks	37 yrs 51%	Triamcinolone AQ 220 mcg vs beclomethasone 336 mcg	-1.71 vs -1.79, NS
Berger 2003 N=295 3 wks	31.6 yrs 62%	Triamcinolone AQ 220 mcg vs Fluticasone 200 mcg	-2.4 vs -2.5, NS
Gross 2002 n=352 3 wks	38.8 yrs 66.5%	Triamcinolone AQ 220 mcg vs Fluticasone 200 mcg	-2.4 vs -2.5, NS

RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire

Nine trials included an analysis of the mean percentage change in severity of eye symptoms.[12, 13, 16-19, 22, 24, 25] Out of those nine trials, only five reported the raw data for comparison of numerical reduction in symptom severity.[12, 13, 16, 18, 25] Differences between nasal corticosteroids were only reported in one of these trials and findings indicated that flunisolide was superior to placebo in the treatment of ocular symptoms ($p<0.05$)[12] Otherwise, nasal corticosteroids generally improved eye symptoms better than placebo; however, when the reduction in eye symptoms is compared to the reduction for other symptoms of SAR it tends to be less dramatic. This trend may indicate that nasal corticosteroids may need be used in combination with other medications for the treatment of ocular symptoms associated with SAR.

2. Trials of SAR patients with NCS formulations unavailable in the US

There were very few differences between nasal corticosteroids across eleven head-to-head trials that involved either an aerosol or dry powder formulations that are not currently available in the US. There were 5 single-blind trials [29-33], 1 double-blind trial,[34] 2 double-blind, double-dummy design trials,[35, 36] 2 open-label trials,[37, 38] and one study in which the patients and investigators were not blinded to the type of treatment due the drug delivery mechanism but a matching placebo was used to create blinding between active and placebo treatment for each drug.[39] The median number of patients in each trial was 60 with a range of 40 to 318. The duration of treatment ranged from 2 to 7 weeks.

There were three trials which compared aerosol formulations of budesonide and beclomethasone,[31, 33, 35], two trials compared budesonide aqueous with budesonide aerosol formulation,[30, 34] two trials compared flunisolide (original formulation) with beclomethasone aerosol formulation,[29, 38] one trial compared budesonide aerosol and dry powder formulation,[37] one trial compared beclomethasone aerosol versus aqueous,[36] and one trial compared flunisolide aqueous to budesonide aerosol formulation.[32]

The results of the three trials that compared aerosol formulations of budesonide and beclomethasone were as follows: one trial found that budesonide provided superior clinical potency to beclomethasone in that smaller doses were required to maintain good

control of symptoms,[35] another trial found that budesonide provided a greater reduction in total nasal symptoms, sneezing and nasal itching than beclomethasone. In an overall assessment of efficacy budesonide produced "very good" results in a larger number of patients than beclomethasone. ($p<0.05$) This trial required patients to use beclomethasone four times daily versus twice daily budesonide. Compliance was not assessed and randomization and allocation concealment consisted of the nurse dispensing the drug to the patients in a random fashion. Baseline characteristics, other than age and gender, were not reported.[33] The final trial compared beclomethasone and budesonide aerosol 200 mcg twice daily. The author concluded that there were no statistically significant differences between the two drugs except during a one-week period in which budesonide-treated patients experienced less sneezing.[31]

Two trials assessed the safety and efficacy of budesonide aqueous versus aerosol formulation and found that both formulations were safe and efficacious.[30, 34] One of the trials concluded that budesonide given once daily as 256 mcg or 400 mcg in an aqueous suspension or as 200 mcg twice daily in an aerosol provided alleviation of symptoms.[34] The other trial reported that the daily dosage of 400 mcg in both preparations proved more efficacious than 200 mcg daily dose in nasal pump spray.[30]

Of the two trials examining budesonide versus flunisolide, one was open-label and the results will not be reported.[38] The other trial reported that there was no difference between the two treatments in daily symptom scores nor overall efficacy.[29]

The only trial that compared fluticasone aqueous to budesonide dry powder revealed that the two treatment were equally effective in reducing nasal symptoms with the exception of blocked nose, in which fluticasone was more effective.[39] The authors of the single trial that compared flunisolide to budesonide aerosol found no significant differences between the medications despite using a dose of flunisolide which was less than the recommended starting dose.[32] Finally, beclomethasone aqueous and aerosol were compared in a 2 week long trial. The authors concluded that there was no difference in efficacy between the two formulations.[36]

Overall, there were no strong clinically significant findings that one product was superior to another. The trials which did report a statistically significant difference it was either with one symptom or with one symptom and for a very short period of time. The other trial which reported statistically significant differences had some design flaws that prevented this finding from being clinically significant.

D. Results of prophylaxis trials of adults with SAR

Mometasone is the only nasal corticosteroid FDA-approved for prophylaxis of SAR and was associated with significantly lower levels of rhinitis symptom severity in the peak- and pre-seasons relative to beclomethasone in the only head-to-head trial of SAR prophylaxis. This double-blind, parallel-group trial was conducted throughout nine centers in the United States for adult and adolescent patients ranging in age from 12 to 69 years of age.[24] The patients were required to be free of symptoms (nasal and non-nasal) at the baseline visit in order to be randomized to receive either beclomethasone 168 mcg twice daily or mometasone 200 mcg once daily plus placebo in the evening for 8 weeks. The patients in this trial starting taking the nasal corticosteroids, on average, 23 days before the onset of ragweed season and recorded the severity of their symptoms twice

daily in a diary. A physician evaluated the severity of the patient's symptoms at screening, day 1 (baseline) and days 8, 22, 29, 36, 50 and 57. The patients in the mometasone and beclomethasone groups had comparable severity scores at baseline, however, the mometasone group had a lower mean nasal symptom score from baseline to the start of the season when compared to beclomethasone treated patients. This is significant because the patients started taking the medication before the start of pollen season and so the mometasone may have conferred some early benefit for patients. The authors concluded that the proportion of minimal symptom days (total nasal symptom score ≤ 2) were equivalent between treatment groups at all time points assessed.

II. Children with SAR

A. Direct comparisons

Physician-rated total nasal symptom score reductions were similar for mometasone and beclomethasone after 4 weeks in the only HTH trial of children with SAR (n=679) (Evidence Tables 1 and 2).[40] One fair-good rated, double-blind, parallel group, placebo-controlled, RCT conducted in pediatric patients, compared three doses of mometasone to beclomethasone [40]. There were 679 patients, who ranged in age from 6 to 11 years old, enrolled in the 4 week trial which took place in 20 centers throughout the United States. Patients were randomized to receive mometasone 25, 100, or 200 mcg daily, beclomethasone 84 mcg twice daily, or placebo. The patients or guardians recorded nasal and non-nasal symptoms in a diary twice daily using a 5-point scale (1=complete relief and 5=treatment failure). Thirty-three patients withdrew from the study, 14 patients (2%) due to adverse events. The mean reduction in physician-rated total nasal symptom score at day 8 did not demonstrate any difference between the three mometasone doses nor between mometasone and beclomethasone. However, between days 16 and 29, patients treated with mometasone 100 and 200 mcg daily improved, whereas those treated with mometasone 25 mcg demonstrated little further reduction of symptoms. By day 29, mometasone 100 and 200 mcg daily and beclomethasone were significantly more effective at reducing symptoms than mometasone 25 mcg daily. Mometasone 200 mcg did not offer any benefit over mometasone 100 mcg daily at any point during the study.

B. Indirect Comparisons

Placebo-controlled trials were evaluated for potential indirect comparisons to address the dearth of head-to-head trials in children (Evidence Tables 3 and 4). Fluticasone 100 or 200 mcg,[41-45] triamcinolone 110 or 220 mcg,[46, 47] flunisolide 150 or 200 mcg,[48, 49] and beclomethasone 42 mcg[50] were all associated with significantly greater levels of symptom relief relative to placebo in two- to four-week, fair-quality trials in pediatric patients with seasonal allergic rhinitis (Table 7). Patients were mostly male and mean ages ranged from 8.3 to 10.5 years in all but one trial.[41] One trial of fluticasone involved 243 adolescents with a mean age of 14.2 years.[41] Eligibility for all trials required positive skin prick tests to a variety of allergens. Extreme heterogeneity in

outcome reporting methods across trials precluded any quantitative analyses of indirect comparative efficacy.

Table 7. Main results in placebo-controlled trials in children with SAR

Study Sample size	NCS (total daily dose) x duration (wks)	Mean age % male	Main Results	Skin tests
Kobayashi 1989 N=101	Beclomethasone 168 mcg x 3	8.8 yrs 68%	Significant decline in nasal obstruction, rhinorrhea, sneezing and nasal itch as rated by physicians and patients (data NR)	Pollen
Strem 1978 N=48	Flunisolide 150 mcg x 4	10.5 yrs 71%	All symptoms combined absent or questionably noted (# days): 5.6 vs 1.2; p<0.0001 Patient felt spray achieved 'total control' (% pts): 16.7% vs 4.2%; p=0.0011	Ragweed pollen
Gale 1980 N=35	Flunisolide 200 mcg x 4	9.7 yrs 74%	Substantial or total control (% pts): 64% vs 33%; p<0.05 Individual symptom relief: sneezing=NS; stuffy nose p<0.05; runny nose p<0.05; eye itch=NS	Grasses in Australia
Boner 1995 n=143	Fluticasone 100 or 200 mcg QD x 4	8.3 yrs 72.7%	Percentage of symptom-free days: Sneezing=55% vs 42% vs 22%; p<0.05 Rhinorrhea=70% vs 59% vs 30%; p<0.05	Known seasonal allergen relevant to geographic area
Galant 1994 N=249	Fluticasone 100 or 200 mcg QD x 4	8.5 yrs 64%	'Significant improvement' (% pts; clinician-rated): 29% vs 35% vs 11%; p<0.01 'Magnitude' of improvement (% reduction in pt-rated mean total nasal symptom scores): 50-57% vs 37%; p<0.05	Local autumn allergen
Grossman 1993 N=250	Fluticasone 100 or 200 mcg QD x 2	8.9 yrs 65%	'Significant improvement' (% pts; clinician-rated): 29% vs 21% vs 9%; p<0.002	Late summer or autumn allergen
Munk 1994 N=243	Fluticasone 100 Fluticasone 200 x 2	14.2 yrs 97%	'Significant improvement' (% pts; clinician-rated): 33% vs 32% vs 9%; p<0.001	Spring allergen
Schenkel 1997 N=223	Triamcinolone 110 or 220 mcg x 2	9 yrs 65.9%	Adjusted mean change from baseline in Nasal Index: -2.62 vs -2.50 vs -1.78; p<0.05	Spring grass allergen
Banov 1996 N=116	Triamcinolone 220 mcg QD x 2	9 yrs 63.7%	Adjusted mean change from baseline in Nasal Index: -2.30 vs -1.16; p<0.05	Grass allergens

Perennial Rhinitis

I. Adults with PAR

A. Results of literature search

We identified nineteen head-to-head trials that compared efficacy of two nasal corticosteroids for perennial allergic rhinitis (Evidence Tables 5 and 6).[11, 51-68] No good quality study was found. Eleven studies were rated fair quality[11, 51-60] and eight studies were rated as poor.[61-68] Table 8 summarizes the combinations of comparisons. We found seven fair quality head-to-head trials comparing efficacy of beclomethasone to other nasal steroids,[51-55, 57] five comparing fluticasone to others,[11, 53, 54, 56, 58] five trials that compared budesonide to another nasal steroid,[11, 55, 56, 59] three studies examining differences between mometasone to older treatments,[57-59] one study comparing old and new formulations of flunisolide[60] and two trials that compared flunisolide to beclomethasone.[51, 52] There were no head-to-head trials comparing efficacy of triamcinolone to any of the other nasal corticosteroids for perennial rhinitis that met the inclusion criteria and were at least of fair quality.

Table 8. Head-to-head trial comparisons

	BDP	*FN*	*TAA*	*FP*	*MF*	BUD
BDP		**4**	**3**	**3**	**1**	**2**
FN		**1**				
TAA						
FP					**1**	**2**
MF						**2**
BUD						

BDP=beclomethasone dipropionate, FN=flunisolide, TAA=triamcinolone acetonide, FP=fluticasone propionate, MF=mometasone furoate, BUD=budesonide

B. Description of trials

The studies for perennial and mixed allergic rhinitis were generally similar in design, inclusion/exclusion criteria, population and duration, but did vary greatly in size. No good quality study was found. Eleven studies were rated fair quality [11, 41, 51-60] and eight studies were rated as poor.[61-68] Poor quality ratings were due to the presence of combinations of multiple serious flaws including inadequate reporting of methods of randomization and allocation concealment, differences between group demographic and prognostic factors at baseline, and exclusion of patients from outcome assessments.[61-68]

All but one[52] of the trials comparing beclomethasone to flunisolide were randomized. Six of these studies were double-blinded,[11, 53, 54, 57, 58, 60] three were open-label,[51, 52, 55] and two did not report blinding methods.[56, 59] Most of these trials were multicentered, while four were performed at a single center.[51, 52, 55, 56]

The populations studied were young to middle aged adults with mean ages mostly around 30-40 years and with balanced numbers of male/female subjects; three studies

reported >60% females [52, 56, 60] and one reported <30% females.[55] Several trials did, however, include adolescents between 12-18 years.[53, 54, 56-58] All trials included patients with perennial rhinitis determined clinically or using various allergy tests and some also reported the proportion of participants with concomitant seasonal allergic rhinitis.[51, 57, 58] The studies varied widely in size from as few as 24 patients to as many as 548 patients. Most studies involved over 300 patients.[11, 53, 57-60] Duration of the trials ranged from three weeks to one year, with most around 4-8 weeks.

Most studies reported receiving financial or personnel support from pharmaceutical companies with the exception of two trials that did not report any source of external support.[55, 56]

C. Results of treatment

1. Direct comparisons

The only evidence suggesting superiority of any one nasal corticosteroid over another comes from one 6-week trial of 273 patients with perennial allergic rhinitis in which budesonide aqueous 256 mcg was associated with a significantly greater mean point reduction in a combined nasal symptom score relative to fluticasone aqueous 200 mcg (-2.11 vs -1.65, p=0.031).[11] Perennial allergic rhinitis symptom reductions appeared similar between nasal corticosteroids when compared at equivalent dosages in most other trials (Table 9).[53, 57-59] The one exception is that fluticasone aqueous 400 mcg/day appeared superior to relatively lower dosages of beclomethasone aqueous (400 mcg/day) in reducing individual symptoms (nasal discharge, nasal blockage, eye watering and irritation, nasal itching, sneezing) over the duration of a year in the longest of the head-to-head trials.[54] The disparity of dosage levels between treatments used in this trial raise questions about how to interpret this finding, however.

Table 9. Reductions in nasal symptom scores in head-to-head trials of PAR patients

	Beclomethasone AQ	Budesonide AQ	Mometasone AQ	Fluticasone AQ
Beclomethasone AQ		Unknown	Similar[57]	Mixed[53, 54]
Budesonide AQ			Similar[59]	**Budesonide superior**[11]
Mometasone AQ				Similar[58]
Fluticasone AQ				

It is unknown how the new[52] or old[51] forms of flunisolide 200 mcg compare directly to the new aqueous form of beclomethasone because both have only been compared to the discontinued aerosol form of beclomethasone 400 mcg in 4-week trials. No other head-to-head trials comparing either form of flunisolide directly to any other nasal corticosteroid in PAR patients were identified. The new and old forms of flunisolide were compared directly to eachother in one 4-week trial and both were

associated with similar reductions in individual symptom scores (sniffing, stuffiness, sneezing, postnasal drainage).[60] No fair- to good-quality trial of the *direct* comparative efficacy of triamcinolone relative to other nasal corticosteroids was identified.

Although most studies used a similar efficacy outcome assessment, it was not possible to make broad indirect comparisons across trials due to differences in reporting methods and availability of detailed data (Table 10). Nine out of the ten studies measured efficacy outcomes using a 4-point scale to describe the severity of individual nasal and non-nasal symptoms with 0=none and 3=severe and one trial used a visual analog scale from 1-100 for two separate individual symptoms.[53] However, reporting methods for primary outcome measures varied widely among the trials, which prevents valuable indirect comparisons. These methods include reductions in points for individual symptoms and composite scores of individual symptoms, percent reduction of individual and/or composite scores and mean daily scores. The composite scores such as Nasal Index Score and Total Nasal Symptom Score include all or some of the measured individual symptoms. In addition, the trials reported physician assessments of symptoms, global evaluation of clinical efficacy and acceptability, onset of action and amount of rescue medication required as secondary outcomes.

Beclomethasone vs. fluticasone

Mixed findings were reported across two head-to-head trials comparing efficacy of beclomethasone to fluticasone (Table 10).[53, 54]. While one study comparing equivalently low doses of the two drugs found no significant differences in total symptom score,[53] the other trial found that a standard dosage of fluticasone (200 mcg) was superior to a relatively lower dosage of beclomethasone (200 mcg) in reducing most individual symptoms.[54]

The British multicenter trial compared non-equivalent doses of the drugs (beclomethasone 200µg to fluticasone 200µg both twice daily) for up to 1 year in 242 patients.[54] The population included adolescents aged 16 and over and adults with perennial rhinitis on the basis of clinical history and not an allergy test. There was no composite symptom score reported but only individual symptom scores for nasal and non-nasal symptoms. Results showed that fluticasone had significantly better symptom grades for nasal discharge, nasal blockage and eye watering and irritation than beclomethasone.

The other study compared fluticasone 100µg either once or twice daily to beclomethasone 168µg or placebo twice daily in 466 adolescents as young as 12 years and adults for 6 months.[53] The outcome measures were expressed as reduction of total symptom scores using a visual analog scale (0-100 for each of four nasal symptoms). The study found no significant differences in efficacy between any of active drugs, both of which showed at least 45% reduction in total symptom score. It was noted that equivalent dosages of beclomethasone (400 µg) and fluticasone (200µg) also had similar efficacy and safety in an unpublished 4-week randomized double-blind placebo-controlled parallel group trial of 286 adult patients with perennial rhinitis that was identified in the dossier provided by the manufacturer of fluticasone.[69] Drop-out rates for beclomethasone, fluticasone 100 mcg and 200 mcg and placebo (28% vs 23% vs 14% vs 28%) in the published trial were noted to be relatively higher than in other similar trials.

Mometasone

Mometasone was associated with generally similar reductions in rhinitis symptoms relative to beclomethasone[57] and fluticasone[58] across two head-to-head trials (Table 10). One double-blind RCT compared beclomethasone 400µg twice daily to mometasone 200µg once daily in 427 adults and adolescents as young as age 12 with perennial allergic rhinitis [57]. The study population included 45-54% patients with seasonal allergies and 18-24% with concomitant asthma. The primary outcome in this 12-week study was measured with mean percent reduction in total morning and evening symptom scores within the first 15 days.

A trial comparing fluticasone to mometasone revealed mixed results for differences in efficacy.[58] One double-blind multicenter RCT compared fluticasone 200µg to mometasone 200µg in 550 adults and adolescents as young as 12 years with confirmed perennial allergic rhinitis. This fair-quality 12-week study included 37.5% patients with concomitant seasonal allergies. The primary outcome of mean percent reduction in total nasal symptom score had to be estimated from figures provided in the article. Although mometasone resulted in greater reduction of the total nasal symptom score, this patient-rated outcome was not significantly different between the two drugs. There was, however, a significantly greater reduction in the some physician-rated secondary outcomes of nasal congestion, nasal discharge, and overall condition with mometasone.

Budesonide

One trial found budesonide to be more efficacious in treating combined nasal symptoms than fluticasone (Table 10).[11] This 6-week Canadian/Spanish study investigated budesonide 256µg versus fluticasone 200µg versus placebo in 273 adults with confirmed perennial allergic rhinitis [11]. There was a significantly greater reduction in combined nasal symptoms scores with budesonide (-2.11 vs. –1.65, p=0.031). Moreover, they found that budesonide was significantly better than placebo at reducing nasal blockage than was fluticasone, while improvement in all other individual symptom scores was similar for both drugs. The onset of action, measured in hours before significant step-score reductions, was quicker for budesonide than fluticasone (36h vs. 60h). The secondary outcome of percentage of patients who reported substantial or total symptom control did not differ significantly between the two drugs.

The only head-to-head study investigating budesonide and mometasone for perennial rhinitis found the two drugs comparable for nasal symptom scores and overall symptom control. One fair-quality European RCT compared budesonide 256µg or 128µg to mometasone 200µg or placebo in 438 adults with confirmed perennial allergic rhinitis [59]. The primary efficacy outcome, nasal symptom score (morning and evening combined) was not significantly different in the two medications. Furthermore, there was no statistically significant difference for the secondary outcomes: percentage of patients experiencing no symptom control, consumption of rescue medication and onset of action. We have identified unpublished quality of life data from this study in the dossier supplied by the manufacturer of budesonide that found no significant differences between treatments except budesonide is superior to placebo for general health and vitality.

Flunisolide: New versus old formulations

The randomized double-blind parallel-group study compared two different formulations of flunisolide aqueous in 215 patients with confirmed perennial allergic rhinitis and found similar efficacy in both treatments [60]. Dosages were equivalent in both the old and new formulations, which reduced propylene glycol from 20% to 5%, increased polyethylene glycol from 15% to 20% and added 2.5% polysorbate in an effort to reduce nasal stinging and burning. There were no significant differences in mean reduction of total symptom and individual symptom scores between formulations. Further, patients rated acceptability of nasal burning/stinging on a 100-point visual analog scale. The original formulation had a mean score of 52 while the new formulation was rated as 87 ($p<0.001$).

Table 10. Outcomes in head-to-head trials of PAR patients

Study Sample size	Interventions (Total Daily Dose) Duration	Mean age % female	Outcome	Results
Sahay 1980 n=60	Flunisolide aerosol BID (200 µg) **Beclomethasone aerosol** QID (400 µg) 4 weeks	37 years 48%	Reduction in mean symptom scores: (A) Sneezing (B) Stuffiness (C) Runny nose (D) Nose blowing (E) Post-nasal drip (F) Epistaxis	(A) –1.44 vs –1.57 (B) –1.74 vs 1.62 (C) –1.33 vs 1.48 (D) –1.70 vs –1.72 (E) –0.74 vs –0.68 (F) –0.15 vs –0.07 NS for all
Bunnag 1984 n=45	Flunisolide BID (200 µg) **Beclomethasone aerosol** QID (400 µg) 4 weeks, then crossover	28.5 years 66.7%	Overall symptom score	-2.91 vs -4.96; p<0.0005
van As 1993 n=466	Fluticasone aqueous BID (100 µg) Fluticasone aqueous QD (200 µg) **Beclomethasone aqueous** BID (168mcg) 6 months	36.3 years 51.3%	Reduction in Total Symptom Score (0-200)	≥ 45% for all (data NR), NS
Haye 1993 n=242	Fluticasone aqueous BID (200 µg) **Beclomethasone aqueous** BID (200 µg) ≤ 1 year	37.6 years 56.6%	No overall score; only: (A) Nasal Discharge (B) Nasal Blockage (C) Eye watering and irritation (D) Nasal itching (E) Sneezing	Fluticasone > beclomethasone (data NR) (A) p=0.002 (B) p=0.002 (C) p=0.048 (D) p=0.052 (E) p=0.114
Al-Mohaimeid 1993 n=120	Budesonide BID (400 µg) **Beclomethasone** BID (400 µg) 3 weeks	30 years 27.5%	(A)Mean daily symptom scores(blocked nose, runny nose, itchy nose, sneezing, runny eyes, sore eyes) (B) % patients symptom free	(A) no differences for all but sneezing: 0.48 vs 0.72, p=0.05 (B) 35% vs 26%; NS
Day 1998 n=273	Budesonide aqueous QD (256 µg) Fluticasone aqueous QD (200 mg) 6 weeks	30.8 years 54.9%	Reduction in combined nasal symptom scores	-2.11 vs –1.65; p=0.031
Tai 2003 n=24	Budesonide QD (400 µg) Fluticasone QD (200 µg) 8 weeks	40.9 years 62.5%	Reduction in Total Nasal Symptom Score (points)	8.01 (87.1%) vs 7.77 (86%) NS

Study Sample size	Interventions (Total Daily Dose) Duration	Mean age % female	Outcome	Results
Drouin 1996 n=427	Mometasone aqueous QD (200 µg) **Beclomethasone aqueous** BID (400 µg) 12 weeks	31.7 years 45.4%	Mean % reduction in total AM + PM symptom diary scores (estimated from figure)	46% vs 51%, NS
Mandl 1997 n=550	Mometasone aqueous QD (200 µg) Fluticasone aqueous QD (200 µg) 3 months	33.0 years 54.7%	Mean percent reduction in total nasal symptom score (estimated from figure)	61% vs 55%, NS
Bende 2002 n=438	Mometasone aqueous QD (200 mg) Budesonide QD (256 µg) Budesonide QD (128 µg) 4 weeks	31.0 years 57.7%	Reduction in Nasal Index Score (morning/evening)	–1.26/-1.44 vs -1.45/-1.59 vs –1.41/-1.50; NS
Meltzer 1990 N=215	Flunisolide aqueous original formulation BID (200mcg) Flunisolide aqueous new formulation BID (200mcg) 4 weeks	33.1 years, original group 62% 34.3 years, new group 66%	Mean Reduction of Total Symptom Score, estimated from figure	-3.0 vs. –2.5, NS

Triamcinolone

Evidence was insufficient for analyzing the comparative efficacy of triamcinolone relative to any other nasal corticosteroids. The only evidence identified for triamcinolone was one unpublished trial and placebo-controlled trials. The unpublished open-label randomized parallel group 3-week trial of 175 patients with perennial rhinitis comparing triamcinolone 220µg to fluticasone 200µg once daily reported no significant differences in efficacy or safety endpoints.[69]

The only other evidence for triamcinolone comes from four large (n=178 to 305) fair quality placebo-controlled trials that assessed triamcinolone in patients with perennial allergic rhinitis and one very small study of cat allergic patients (n=12) [70-74]. All of the larger studies reported significantly lower nasal symptoms for the active drug in treatment of perennial rhinitis. Storms et al investigated 3 different doses of triamcinolone aerosol (110µg, 220µg and 440µg/day) vs. placebo in 305 patients and found nasal index (composite of 4 symptoms on 4-point scale, maximum 12 points) values after 12 weeks (weekly mean change from baseline) of -2.9, -3.5, -3.35 and -2.2 respectively, $p<0.05$ [70]. Another study of 296 patients with mixed allergic rhinitis reported –4.80 vs. –3.55, ($p<0.001$) significant reduction of mean score of daily total symptom score (maximum score 20 points, 5 symptoms on a 5-point scale) for triamcinolone aqueous 220µg and placebo respectively [71]. Potter et al also reported significant improvements in a Rhinoconjunctivitis Quality of Life Questionnaire in the areas of sleep, nasal symptoms, emotional problems and overall QoL compared to placebo [71]. The 12-week PCT of 205 perennial rhinitis subjects taking triamcinolone aerosol 200µg reported change from baseline nasal index (maximum 9 points) –3.16 vs. -2.36, $p<0.05$ for active drug and placebo respectively [73]. A 4-week PCT of triamcinolone aqueous 220µg in 178 patients with perennial allergic rhinitis showed a significant overall reduction in nasal index (sum of three individual symptom scores, 4-point scale,

0=none and 3=severe) for triamcinolone compared with placebo, -2.07 vs. 1.27, p<0.02 [74]. The 1-week crossover trial of triamcinolone 220µg followed by a 1-hour cat allergen challenge resulted in mean nasal symptoms (4-point scale, 0=none and 3=severe) of 0.65 vs. 1.0, p=0.06 for active drug and placebo respectively [72].

Trials of NCS drugs unavailable in the US

Beclomethasone aerosol. New and old forms of flunisolide 200 mcg have only been compared directly to the discontinued aerosol form beclomethasone and evidence was inconsistent across these trials.[51, 52] Two fair-quality trials compared beclomethasone to flunisolide for perennial rhinitis [51, 52]. One study found no significant differences between treatments and the other concluded that beclomethasone was superior to flunisolide in reducing overall symptom score.[51, 52] The first trial is a 4-week single-center open British RCT comparing 400µg metered aerosol dose beclomethasone to 200µg metered pump flunisolide in 60 patients suffering from perennial allergic rhinitis with about three quarters of the participants reporting concomitant seasonal allergic rhinitis and over half reporting concomitant asthma [51]. There was no significant difference found in the reduction of mean scores of individual symptoms between the medications. The other trial is a 4-week single-center open non-randomized Thai crossover study of the same doses of beclomethasone and flunisolide as the previous trial in 45 patients with perennial allergic rhinitis with only 8.3% concomitant asthma [52].This study demonstrated a significantly greater reduction in overall symptom score for beclomethasone vs. flunisolide (-4.96 vs. -2.91, p<0.0005). However, when asked to rate the effectiveness of the treatments, neither patients nor physicians reported a significant difference between the two drugs in this study.

Another trial compared budesonide to the discontinued, aerosol form of beclomethasone.[55] This fair-quality 3-week open trial examined beclomethasone 400µg twice daily vs. budesonide 400µg twice daily in 120 adult patients.[55] The study population was somewhat different from the others with 72.5% men suffering from perennial rhinitis, which was determined by clinical history only. Primary outcomes were mean daily symptom scores for individual nasal and non-nasal symptoms. There were no significant differences between medications except for sneezing, which were less for budesonide than for beclomethasone (0.48 vs. 0.72, p=0.05). Secondary outcomes that measured the percentage of patients that were symptom-free at 3 weeks showed no significant difference.

Finally, an 8-week Taiwanese study compared budesonide powder 400µg to a form of fluticasone 200µg that is not available in the US (Flixonase®).[56] This trial randomized 24 adults and adolescents at least 16 years old with confirmed moderate to severe perennial allergic rhinitis [56]. Efficacy was measured with reduction in total nasal symptom score and there was no evidence of a significant difference between budesonide and fluticasone.

II. Adolescents and children with PAR

A. Direct comparisons

Beclomethasone vs. fluticasone

We found one head-to-head efficacy trial comparing fluticasone aqueous to beclomethasone aqueous in children that satisfied the criteria of the review (Evidence Tables 5 and 6).[75] The comparative part of this investigation revealed no differences in efficacy between treatments. This study combined data from a smaller (n=120) 12-week head-to-head trial comparing fluticasone 100µg once or twice daily with beclomethasone 200µg twice daily with data from a larger (n=415) 4-week placebo-controlled trial, which compared fluticasone 100µg or 200µg once daily with placebo. Efficacy was reported as median percent of symptom-free days for sneezing, rhinorrhea and congestion as scored by patients and assessed by investigators. There is no specific data reported for the comparator study, only the statement that fluticasone was as effective as beclomethasone in increasing the median percent of symptom-free days for all symptoms. The placebo-controlled trial also reported no specific data, but only greater or less median percentage of days free of each of the three symptoms with p values. Sneezing and rhinorrhea received significantly better scores by patients taking fluticasone when compared with placebo, however, nasal blockage showed no statistical significance in median rate of symptom-free days. There was no significant dose response in efficacy for fluticasone treatment groups.

B. Indirect comparisons: Placebo-controlled trials

Since there was only one head-to-head comparison study involving children or adolescents that met review criteria, we looked at the available evidence from 10 placebo-controlled trials (Evidence Tables 7 and 8; Table 11).[76-85]. Due to the heterogeneity of this evidence, no indirect comparisons of efficacy in children were possible.

Table 11. Placebo-controlled trials in children/adolescents with PAR

Study Sample size	Interventions (Total Daily Dose) Duration	Mean age Age range % female	Outcome	Results
Day 1990 n=51	Budesonide BID (200 µg) Placebo 4 weeks	13.4 vs 13.3 years, 7-18 vs 6-18 years 53.4% vs 40%	Difference in combined nasal symptom scores, including Sneezing, blocked nose, itchy nose, runny nose	-0.95 ± 1.87 vs -0.37 ± 1.38 p < 0.05
Fokkens 2002 n=202	Budesonide aqueous QD (128 µg) Placebo 6 weeks	10.5 vs 10.7 years, 6-16 years, 34.3%	Difference in combined nasal symptom scores (evening), including Sneezing, blocked nose, runny nose	-1.86 vs -0.93; p<0.001

Study Sample size	Interventions (Total Daily Dose) Duration	Mean age Age range % female	Outcome	Results
Hill 1978 N=22	Beclomethasone aerosol QD (300 µg) Placebo 6 weeks then crossover	NR, 7-17 years, 50%	% children with improved nasal symptoms (lower mean daily diary score)	86.4% p<0.01 placebo results not reported
Shore 1977 N=46	Beclomethasone aerosol (300 µg) Placebo 3 weeks then crossover, followed by 3 months open label with active drug (200 µg)	8 years, 4-12 years, 21.7%	Patient assessment that drug was effective	75% placebo results not reported
Neuman 1978 N=30	Beclomethasone aerosol four times daily (200 µg) Placebo 3 weeks then crossover	13.8 years, 9-18 years, 53.3%	Difference (baseline to end of study) Average daily symptom score on 4-point scale	Group I –2.5 vs 0 Group II –2.5 vs +2.65 (no washout period!)
Ngamphaiboon 1997 N=106	Fluticasone aqueous QD (100 µg) Placebo 4 weeks	8.96 vs 9.06 years, 5-11 years, 18.9% vs 10.3%	Physician-rated mean total symptom score (sum of obstruction, rhinorrhea, sneezing and itching, scale 0-3)	-6.13 vs –5.7, p<0.05
Todd 1983 N=64	Flunisolide aqueous QD (150 µg) Placebo 4 weeks then crossover	8.3 years, 3-17 years, 39%	Mean daily total symptom score (stuffy nose, sneezing, runny nose, nose blowing and eye symptoms)	Significantly lower than placebo for Group II only for 11 of 28 days
Sarsfield 1979 N=27	Flunisolide aqueous QD (150 µg) Placebo 2 months then crossover	12.3 years, 7-16 years, 22%	Mean weekly symptom scores on 4-point scale (A) sneezing (B) stuffy nose (C) runny nose (D) nose-blowing	Week 4 (A) 0.64 vs 1.17 (B) 1.04 vs 1.00 (C) 0.62 vs 0.85 (D) 1.10 vs 1.45
Welch 1991 N=210	Triamcinolone aerosol (165 µg) Triamcinolone aerosol (82.5 µg) Placebo 12 weeks	9 years, 4-12 years, 33%	Adjusted mean change from baseline total nasal symptom score in first 6 weeks (no escape medication allowed) and second 6 weeks (escape medication allowed)	Estimated from figure: first 6 weeks 2.65 vs 2.2 vs 1.65 second 6 weeks 3.35 vs 2.75 vs 2.05 p<0.01 for highest dose compared to placebo
Storms 1996 N=137	Triamcinolone aerosol (220 µg) Placebo 4 weeks	8.9 years, 6-11 years, 27% vs 44%	Adjusted mean change from baseline nasal index: sum of symptom scores for nasal stuffiness, nasal discharge, and sneezing each on a 4-point scale	-2.27 vs –1.36, p<0.05
Nayak 1998 N=80	Triamcinolone aqueous (220 µg) Triamcinolone aqueous (440 µg) Placebo 6 weeks	9.5 years, 6-12 years, 37.5%	Outcome not eligible, for adverse events only	

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Perennial Non-allergic Rhinitis—Adults and Adolescents

I. Adults

A. Direct Comparisons

There were no head-to-head efficacy trials that compared any nasal corticosteroids in adults with perennial non-allergic rhinitis that met the inclusion criteria of this review.

B. Indirect Comparisons in placebo-controlled trials

We found two placebo-controlled studies of patients with non-allergic rhinitis that were not indirectly comparable due to heterogeneous efficacy outcome reporting (Evidence Tables 9 and 10). The first study of fluticasone reported efficacy for use in non-allergic rhinitis and the second study of mometasone revealed mixed results in this population.[86, 87].

A pooled analysis from three randomized, double-blind, double-dummy, placebo-controlled trials examining fluticasone aqueous 200µg and 400µg vs. placebo in 983 patients with non-allergic rhinitis with (NARES) and without eosinophilia (non-NARES) reported clinical improvement of symptoms in the total population [86]. Both doses of active drug showed significant improvement in total nasal symptom score (100-point visual analog scale for individual symptoms, maximum possible 300) after 4 weeks compared to placebo, -84, -85 and –64 for the lower dose, higher dose and placebo respectively, $p<0.002$. Differences for the individual subgroups, non-NARES and NARES, also favored active drugs, but did not report significance.

The fair quality multicenter, randomized, double-blind, placebo-controlled trial investigating mometasone 200µg found mixed results for the efficacy in 329 adult patients with non-allergic rhinitis [87]. The patient-rated improvement was numerically greater for mometasone than placebo, 56% vs. 49%, however not found to be significantly different. The secondary efficacy variable of investigator-rated improvement was indeed significantly greater for mometasone compared to placebo, 60% vs. 48% ($p=0.03$). Efficacy was reported as improvement rate, which was defined as reduction of at least one point in overall symptom score, comprising four individual symptoms on a 4-point scale for a maximum total of 12 points. The study also reported no significant difference in quality of life, but did not report methods or specific results.

II. Children with non-allergic rhinitis

No efficacy trials of nasal corticosteroids in children with perennial non-allergic rhinitis were identified.

Key Question 2.
For adults and children with seasonal or perennial (allergic and non-allergic) rhinitis, do nasal corticosteroids differ in safety or adverse events?

All rhinitis types

I. Adults and adolescents

A. Direct comparisons

Head-to-head trials served as the primary source of evidence for comparisons between nasal corticosteroids in incidence and severity of the more common adverse effects associated with shorter-term usage. No head-to-head trial was of sufficient duration to measure comparative risk of cataract development or worsening of glaucoma. Rates of withdrawals due to adverse events, headache, throat soreness, epistaxis and nasal irritation were generally similar between nasal corticosteroids in head-to-head trials of adults/adolescents with either seasonal or perennial rhinitis (Table 12).[11-20, 22-26, 28, 51-55, 57-60, 87-91] One exception is that the old formulation of flunisolide 200 or 300 mcg was associated with significantly higher rates of nasal burning/stinging than beclomethasone AQ 168 or 336 mcg (30% vs 33% vs 10% vs 10%; $p<0.05$)[25] and higher rates than the new formulation of flunisolide 200 mcg (13% vs 0; $p<0.001$)[23] in 4-week trials of adults with SAR. It is not yet clear how the new formulation of flunisolide 200 mcg ranks relative to other nasal corticosteroids with regard to nasal irritation effects. This is because, to-date, nasal burning/stinging rates associated with the new formulation of flunisolide have only been directly compared to the discontinued form of beclomethasone (20% vs 2.2%; $p=0.0081$) in adults with PAR.[52]

The few other differences pertain to rates of headache and epistaxis. In the only trial of nasal corticosteroids used prophylactically, mometasone 200 mcg was associated with significantly higher rates of headache than beclomethasone 336 mcg in an 8-week trial of adults with SAR.[24] Additionally, fluticasone 200 mcg was associated with a significantly higher rate of epistaxis than a relatively lower dosage of beclomethasone 200 mcg (14% vs 5%; $p=0.0285$) after a year or less in a trial of adults with PAR.[54] Fluticasone may have been at a disadvantage in this comparison due to the use of a relatively low dose of beclomethasone. This result was not consistent with three other trials using equivalent dosage comparisons.[15, 20, 53]

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2 **Table 12. Adverse events in head-to-head trials**

Study Sample size Trial duration	Age % female Rhinitis type	Treatments (total daily dose in mcg)	Withdrawals due to adverse events	Headache	Throat soreness	Epistaxis	Nasal Irritation
McArthur 1994 n=77 3 wks	27 yrs 51% SAR	BUD 200 mcg vs BEC 200 mcg	4% vs 0; NS	2% vs 0; NS	2% vs 0; NS	0 vs 2.6%; NS	Itchy nose: 0 vs 2.6%; NS
Al-Mohaimeid 1993 n=120 3 wks	30 years 27.5% PAR	BUD 400 µg vs BEC 400	5.2% vs 1.7%; NS	NR	NR	NR	NR
Zawisza 1992 n=43 4 wks	NR NAR	FLUN 200 vs BEC 300	0% vs 10%	NR	NR	NR	20% vs 40%
Synnerstad 1996 n=25 12 mo	44.1 years 16% NAR	BUD 256 vs BEC 336	NR	NR	NR	0 vs. 25%	8.3% vs 16.6%
Langrick 1984 n=60 7 wks	66.7 yrs 37.5% SAR	FLUN 200 vs BEC 400	None	Dry throat: 2.9% vs 0; NS Tickling sensation in nose: 0 vs 2.8%; NS			
Welsh 1987 n=100 6 wks	28 yrs 33% SAR	FLUN 200 vs BEC 336	6.7% vs 0; NS	0 vs 16.7%; p=0.0522	NR	Nosebleeds: 0 vs 0	Sore nose: 3.3% vs 3.3%; NS
Bronsky 1987 n=151 4 wks	29 yrs 52% SAR	FLUN 200/300 vs BEC 168/336	NR	10% vs 10% vs 12% vs 10%, NS	8% vs 5% vs 5% vs 0%, NS	8% vs 8% vs 7% vs 8%, NS	Stinging/burning: 30% vs 33% vs 10% vs 10%; p<0.05
Sahay 1980 n=60 4 wks	37 yrs 48% PAR	FLUN 200 vs BEC 400	3.3% vs 10%; NS	13.3% vs 3.3%; NS	NR	0 vs 10%; NS	Nasal irritation: 10% vs 3.3%; NS Nasal dryness: 6.7% vs 10%; NS

Study Sample size Trial duration	Age % female Rhinitis type	Treatments (total daily dose in mcg)	Withdrawals due to adverse events	Headache	Throat soreness	Epistaxis	Nasal Irritation
Bunnag 1984 n=45 4 wks	28.5 years 66.7% PAR	FLUN 200 vs BEC 400	2.2% vs 0; NS	2.2% vs 2.2%; NS	NR	NR	Burning sensation: 20% vs 2.2%; p= 0.0081 Nasal irritation: 2.2% vs 0; NS
Conley 1994 n=100 1 day	40.0 years 61% PAR	FLUN 50 vs BEC 84	None	0 vs 2%; NS	NR	NR	NR
Ratner 1992 n=136 2 wks	44 yrs 62% SAR	FLUT 200 vs BEC 336	None	0 vs 1%; NS	2% vs 2%; NS	3% vs 2%; NS	Nasal burning: 5% vs 2%; NS
Laforce 1994 n=238 4 wks	24 yrs 29% SAR	FLUT 200 BID or QD vs BEC 336	0 vs 0 vs 1.6%; NS	4.7% vs 3.6% vs 4.9%, NS	3.1% vs 0 vs 3.3%, NS	0 vs 1.8% vs 4.9%; NS	Burning: 1.6% vs 1.8% vs 6.5%; NS
van As 1993 n=466 6 mo	36.3 years 51.3% PAR	FLUT 200 BID/200 QD vs BEC 168	5% vs 3% vs 9%; NS	4% vs 2% vs 5%; NS		14% vs 15% vs 9%; NS	Nasal irritation: 0 vs 2% vs 0 Nasal dryness: 3% vs 2% vs 0; NS Nasal burning: 1% vs 3% vs 3%; NS
Haye 1993 n=242 ≤ 1 year	37.6 years 56.6% PAR	FLUT 200 vs BEC 200	NR	8% vs 4%; NS	NR	14% vs 5%; p=0.0285	NR
Hebert 1996 n=477 4 wks	32 yrs 8.5% SAR	MOM 100/200 vs BEC 400	3% vs 4% vs 0; NS	8% vs 10% vs 8%; NS	Pharyngitis: 3% vs 2% vs 4%, NS	3% vs 6% vs 5%, NS	NR
Graft 1996** N=347 8 wks	34.7 yrs 47.3% SAR	MOM 200 vs BEC 336	0.8% vs 4.3%; NS	36% vs 22%; p=0.02	Pharyngitis: 6% vs 10%; NS	NR	NR
Drouin 1996 n=427 12 wks	31.7 years 45.4% PAR	MOM 200 vs BEC 400	5.6% vs 4.1%; NS	10% vs 7%; NS	NR	19% vs 23%; NS	Nasal irritation: 3% vs 3%; NS Nasal Burning: 3% vs 3%; NS

Study Sample size Trial duration	Age % female Rhinitis type	Treatments (total daily dose in mcg)	Withdrawals due to adverse events	Headache	Throat soreness	Epistaxis	Nasal Irritation
Lumry 2003 n=147 3 wks	37 yrs 51% SAR	TRI AQ 220 vs BEC 336	None	Respiratory system: 15% vs 10%; skin and appendages: 1% vs 9%; digestive system: 5% vs 5%; nervous system: 4% vs 0; all p=NS			
Stern 1997 n=635 4-6 wks	Age NR 51% SAR	BUD 128/256 vs FLUT 200	0.5% vs 0.5% vs 1.7%; NS	NR	NR	NR	NR
Mandl 1997 n=550 3 mo	33.0 years 54.7% PAR	MOM 200 vs FLUT 200	1% vs 2%; NS	6% vs 9%; NS	NR	17% vs 17%; NS	Nasal burning: 3% vs 3%; NS Nasal irritation: 2% vs 3%; NS
Day 1998 n=273 6 wks	30.8 years 54.9% PAR	BUD 256 vs FLUT 200	1.8% vs 1.8%; NS	9% vs 10%; NS	NR	Bloody nasal discharge: 18% vs 7%; NS	NR
Tai 2003 n=24 8 wks	40.9 years 62.5% PAR	BUD 400 vs FLUT 200	None	NR	NR	NR	NR
Berger 2003 3 wks n=295	31.6 yrs 62% SAR	TRI AQ 220 vs FLUT 200	None	6.8% vs 4.1%, NS	Pharyngitis: 0.7% vs 2.7%; NS	2.7% vs 4.8%, NS	NR
Gross 2002 n=352 3 wks	38.8 yrs 66.5% SAR	TRI AQ 220 vs FLUT 200	1.2% vs 0; NS	11% vs 11.7%; NS	Pharyngitis: 2.3% vs 6.7%; NS	NR	NR
Small 1997 n=233 3 wks	28 yrs 52% SAR	TRI HFA 220 vs FLUT 200	NR	5% vs 9%; NS	NR	3% vs 4%; NS	NR
Bende 2002 n=438 4 wks	31.0 years 57.7% PAR	MOM 200 vs BUD 256/128	4.7% vs 0.9% vs 1.9%; NS	11% vs 11% vs 9%; NS	NR	9% vs 6% vs 6%; NS	NR

Study Sample size Trial duration	Age % female Rhinitis type	Treatments (total daily dose in mcg)	Withdrawals due to adverse events	Headache	Throat soreness	Epistaxis	Nasal Irritation
Ratner 1996 n=218 6 wks	44 yrs 62% SAR	New vs old FLUN 200 mcg	NR	9% vs 5%; NS	NR	NR	Irritation/tenderness: 4% vs 4%; NS
Greenbaum 1988 n=122 4 wks	NR NR SAR	New vs old FLUN 200 mcg	2.4% vs 4.1%; NS	<12% overall; NS between groups (data NR)	Throat irritation: 2% vs 0; NS	NR	Severe nasal burning/stinging: 0 vs 13%; p<0.001

Five head-to-head trials assessed how adverse sensory attributes of nasal corticosteroids use (e.g., overall comfort, medication run-off, irritation, odor, taste) affected patient preferences (Evidence Tables 5 and 6).[92-96] These studies reported no consistent differences between treatments. One trial compared single doses of budesonide aqueous (64µg) with fluticasone (100µg or 200µg) and found differences only in sensory outcomes that were not relevant for this review.[94] No comparative adverse events data were reported. Another trial comparing single doses of triamcinolone aqueous, beclomethasone aqueous and fluticasone aqueous in 94 adult patients with mixed allergic rhinitis showed no significant differences for nasal irritation, urge to sneeze or drug run-off between treatment groups.[96] The remaining three trials compared single doses of triamcinolone aqueous 220µg to fluticasone 200µg and mometasone 200µg [92, 93, 95] and only Stokes and Bachert revealed a significant difference in a relevant outcome. It should be noted that these Stokes used a pooled analysis of two studies and Bachert reported more thoroughly the data from one of these studies. This fair to poor quality study found that triamcinolone aqueous had significantly less nasal irritation in the immediate and delayed (2-5 min.) measurements [93]. Bachert was the only study to report adverse events and found no significant difference between treatments [95].

B. Indirect comparisons

Placebo-controlled trials and observational studies provided the only evidence available of the risk of cataract development and longer-term adverse effects of nasal corticosteroids. Evidence is extremely limited and insufficient for indirect comparisons between nasal corticosteroids.

1. Cataract

We identified one retrospective observational cohort study of cataract incidence in 88,301 patients younger than 70 years of age taking intranasal steroids in England and Wales (Evidence Tables 11 and 12) [97]. Seventy percent of these patients used beclomethasone only. The study compared nasal steroid users to a non-exposed population to determine the incidence rate/1000 person years and the relative risk of developing cataract as a result of treatment. Evidence showed that there was no increase in the relative risk of cataract among all users of nasal corticosteroids (RR 1.0, 95% CI 0.6-1.4) or among beclomethasone users compared with the unexposed (RR 0.8, 95% CI 0.5-1.2).

We are aware of additional unpublished data from a comparative study of mometasone beclomethasone and placebo that found no clinically significant changes in results from ophthalmic exams during the 12-week study period. An unpublished 12-month open-label extension of the previously mentioned study reported no cataract and no significant differences in mean intraocular pressure between treatments groups.

2. Common adverse respiratory and nervous system effects of longer-term use

One open-label 12-month extension of a 4-week randomized placebo-controlled double-blind trial evaluated long-term safety and efficacy of triamcinolone aqueous (200µg with option to reduce to 100µg/day if symptoms are adequately controlled) in 172 patients with confirmed perennial rhinitis [98]. Adverse event rates potentially due to treatment were higher in the extension study than in the original controlled trial: Headache 22.1% vs. 6.8%, epistaxis 18 % vs. 6.8%, pharyngitis 32% vs. 14.8%, rhinitis 28.5 % vs. 6.8%, cough 8.1% vs. 0% and sinusitis 15.7%. The authors note that there is some overlap with the winter cold season and are not all clearly related to treatment with intranasal triamcinolone. The study also reports rates of adverse events related to topical effects possibly related to treatment that although low, are higher in the long-term observation compared with the 4-week trial: nasal irritation 2.3% vs. 0%, nasosinus congestion 1.2% vs. 0%, throat discomfort and dry mucous membranes 0% in both studies, sneezing 0.6% vs. 0% and epistaxis 12.8% vs. 4.5%.

A 12-month, randomized, double-blind, placebo-controlled parallel group trial of 42 patients with confirmed perennial allergic rhinitis of fluticasone aqueous 200µg/day reported only epistaxis as occurring more frequently in the active drug group [99]. There was one withdrawal due to an adverse event in the fluticasone group. Unpublished data from an open-label 52-week observational study of fluticasone 200µg twice daily in 60 patients with perennial rhinitis reported no serious or unexpected adverse events (http://www.fda.gov/cder/foi/nda/98/20121S009_Flonase.htm).

II. Adolescents and Children

A. Direct comparisons

Evidence of the comparative safety of nasal corticosteroids in adolescents and children is extremely limited and comes only from three head-to-head trials. [75, 100, 101] Richards and Milton concluded that there were no clear differences in treatment-related adverse events between fluticasone aqueous, beclomethasone and placebo [75]. There were some numerical differences in epistaxis occurring most frequently with fluticasone 100µg, but they could not be found clinically significant due to relative rarity and varying severity of symptoms. There were also no differences found in rates of withdrawal due to adverse events between treatment groups. The next controlled trial compared mometasone to budesonide in 22 children aged 7-12 years with confirmed perennial, seasonal or mixed allergic rhinitis [100]. There were no withdrawals due to adverse events and no clear differences in rates of adverse events between treatments or active drug and placebo. The study did not report individual adverse events separately for treatment groups. A randomized controlled double/single-blind trial examined two doses of triamcinolone and fluticasone in 49 children between 4-10 years old [101]. This trial studied short-term bone growth and effects of nasal steroids on the hypothalamic-pituitary-adrenal axis, which were not included in our adverse event review, but we were able to include the other clinical adverse events reported. There were no clear differences in all-

cause adverse event rates among the treatment groups, triamcinolone 110µg (50%), triamcinolone 220µg (43.6%), fluticasone (43.6%), placebo (49%). Fever was the only individual adverse event reported for all treatment groups and there were no clear differences among the groups for incidence of fever. There were three withdrawals due to adverse events in the triamcinolone 110µg group, one of which was treatment-related and one withdrawal due to adverse events in the placebo group.

B. Indirect comparisons

Due to the paucity of head-to-head trial evidence in adolescents/children, placebo-controlled trials were analyzed for further assessment of how nasal corticosteroids compare to one another, indirectly, in rates of more common adverse respiratory and nervous system effects and in effects on growth. The only evidence of the efficacy and safety of nasal corticosteroids in preschool-aged children also comes from a placebo-controlled trial.

1. Common adverse respiratory and nervous system effects

All eleven 2- to 12-week placebo-controlled trials reported miscellaneous tolerability outcomes such as nasal irritation, epistaxis/blood-tinged nasal secretions, headache and others in children aged 8.3 to 12.3 years.[76, 77, 81-85, 102-105] and only three studies additionally reported effects on standing height. [102, 103, 105] The reporting of adverse effects in these trials was inconsistent across studies and thus, it is not possible to draw conclusive indirect comparisons. Day et al reported no significant difference of adverse effects between budesonide and placebo [76], a 4-week study found no adverse events with fluticasone or placebo [81] and the remaining nine studies reported no clear differences in adverse effects between the active drug and placebo groups.[77, 82-85, 102-105].

The only evidence of safety in younger children between the ages 2-5 years comes from an unpublished placebo-controlled trial of mometasone that was revealed in our dossier review. There were no serious adverse events found during the 6-week treatment period and headache and rhinorrhea were more common in the placebo group, while upper respiratory tract infection and skin trauma occurred more frequently in children using mometasone.[106]

2. Lenticular opacities

We identified one observational trial that examined long-term safety of budesonide in 78 children with confirmed perennial rhinitis between the ages of 5-15 years [107]. Sixty-eight patients reported adverse events, 23 children had nasal dryness in the first 12 months and 12 had it in months 13-24, 6 children has blood-tinged nasal discharge in the first year and 3 in the second year and 10 reported headaches in the first year and 12 during the second year. There was one serious adverse event, an epileptic seizure that was deemed unlikely to be treatment related. There were four small lenticular opacities found, two were present before study begin and remained unchanged over 24 months of treatment and the other two were transient and disappeared upon continuation of budesonide treatment. There is no report of the clinical significance of these opacities.

3. Growth Retardation in Children

The only evidence of clinical growth effects comes from three randomized double-blind placebo-controlled trials and two observational studies.[102, 103, 105, 107, 108] These studies reported change from baseline in statural growth, although the reporting methods varied somewhat among the studies. The use of short-term lower-leg growth rates measured with kneometry methods is less predictive of long-term growth due to the inconsistent and irregular timing of growth spurts in childhood [103]. Many studies of nasal corticosteroids have included the assessment of hypothalamic-pituitary-adrenal (HPA) axis function in order to determine the systemic effects, however the FDA has suggested that childhood growth may be a more sensitive indicator of these systemic adverse effects than the HPA axis function [105].

Growth effects of beclomethasone AQ 168 mcg, fluticasone AQ 200 mcg and mometasone 100 mcg were each compared to placebo, respectively, all in 12-month randomized controlled trials[102, 103, 105] and beclomethasone[102] was the treatment associated with a significantly higher risk of growth reduction (Table 13). Allen et al reported no significant difference in change of height from baseline between the fluticasone aqueous 200µg and placebo (6.8cm vs. 6.5cm) of children with confirmed perennial rhinitis after 12 months.[103] The study of mometasone 100µg vs. placebo also showed no significant differences in mean height increase over 1 year, 3-5 year-old: 7.65cm vs. 7.26cm and 6-9 year-old: 6.67cm vs. 6.00cm.[105] Finally, Skoner et al found a reduction in growth rate for beclomethasone aqueous 168µg twice daily in children with perennial allergic rhinitis between 6 and 9.5 years of age when compared with placebo, 5.0cm vs. 5.9cm after 12 months.[102].

We are aware of unpublished interim results from a randomized open-label 52-week comparison of budesonide aqueous to cromolyn sodium in children with perennial rhinitis that suggest some progressive slowing of growth in the budesonide group (http://www.fda.gov/cder/foi/nda/96/020233s003_rhinocort_toc.htm).

Evidence from observational studies is inconsistent with the placebo-controlled trials. A retrospective controlled study of 60 children (Age 24-117 months, mean age: 70 months) taking beclomethasone aqueous 336µg/day for confirmed perennial rhinitis investigated medium and long-term growth and found no adverse growth effects [108]. Growth outcomes were expressed as a comparison of annual height velocity with predicted height velocity. Results showed mean height percentile on entry was 44.6 and at the final visit, 52.2. The boys had an actual height growth velocity of 6.66 cm/year vs. predicted height growth velocity of 6.3 cm/year and the girls grew at a rate of 4.66 cm/year vs. the predicted value of 5.25 cm/year. It should be noted that this study was unable to determine compliance rates from the clinical records and the children were allowed to take other antiallergic medication (antihistamines and decongestants) as needed.

Another observational study examined long-term growth rates in 73 children using budesonide over a period of 24 months [107]. They assessed growth by comparing mean height to height predicted at entry. In the first 12-month period 73 children were included and found to have a mean height at entry of 102.5% and 102.2% after 12 months. The difference was not statistically significant. In the cohort that continued until

24 months (n=33), mean height at entry was 102% of predicted and 101.9% at end of study (p=0.45). Thus, they found no significant difference in predicted mean height under the treatment with budesonide.

Table 13. Summary of growth outcomes

Study Sample size Mean age % female	Interventions (Total Daily Dose) Duration	Outcome	Results
Skoner 2000 n=80 7.5 years/7.1 years 31%	**Beclomethasone aqueous** (336 µg) vs. placebo 12 months Randomized, double-blind, placebo-controlled	Mean change in height from baseline	5.0 cm vs. 5.9, p<0.01
Schenkel 2000 n=98 6.3 years 32.7%	**Mometasone aqueous** (100 µg) vs. placebo 12 months Randomized, double-blind, placebo-controlled	Mean change in height from baseline 3-5 years 6-9 years	7.65 cm vs. 7.26 cm 6.67 cm vs. 6.0 cm, both NS
Allen 2002 n=150 6.2 years 34%	**Fluticasone aqueous** (200 µg) vs. placebo 12 months Randomized, double-blind, placebo-controlled	Mean change in height from baseline 3 months completed 12 months completed	6.39 cm vs. 6.30 cm 6.32 cm vs. 6.20 cm, both NS
Mansfield 2002 n=60 5.8 years 33%	**Beclomethasone aqueous** (168-336 µg) Mean treatment duration: 3 years Retrospective observational	Comparison annual growth velocity with predicted growth velocity	Boys: 6.66 cm/y vs.6.0 cm/y Girls: 4.66 cm/y vs. 5.25 cm/y, both NS
Moller 2003 n=78 10.8 years 28%	**Budesonide aerosol and aqueous** (200-600 µg) 24 months Prospective open observational	Mean height percent of predicted at entry vs. actual mean height percent First 12 months - aerosol Second 12 months - aqueous Mean change in height from baseline First 12 months - aerosol Second 12 months - aqueous	102.5% vs. 102.2% 102.1% vs. 101.9%, NS for both 4.9 cm 5.2 cm

Key Question 3.
Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities, or in pregnancy and lactation for which one nasal corticosteroid is more effective or associated with fewer adverse events?

No studies stratified or analyzed data by subgroups of patients based on demographics, use of concomitant medications, or comorbidities. Race was only reported in one-third of all head-to-head trials and was generally predominantly Caucasian.[13, 18, 22, 24-26, 55, 88, 94, 101] Use of other concomitant nasal medications and/or presence of other concurrent nasal pathologies (e.g., sinusitis, viral infections, nasal structural abnormalities) were generally exclusionary. Given these limitations, the demographic, concomitant medication usage and comorbidity data provided can only be useful in determining the generalizability of results, but do not provide many insights into potential differences in efficacy or adverse events.

I. Demographics

Most head-to-head trials conducted in adults were comprised of comparable proportions of males (52%) and females (48%) and mean age overall was 33.5 years (range 24 years to 66.7 years). There were a few exceptions. One 4-week trial of mometasone 100 or 200 mcg and beclomethasone 400 mcg involved 477 adults with SAR that were almost all male (91.5%).[28] Indirect comparisons suggest that physician ratings of improvement and changes in total symptom scores were similar in this trial to other similar trials with higher proportions of female participants. In another trial of flunisolide 200 mcg versus beclomethasone 400 mcg in adults with SAR and a noticeably higher mean age of 66.7, however, rates of physician-rated improvement were numerically lower than in other similar trials of younger patients. It is not possible to draw conclusions about potential differential effects based on age using data from this trial, however, as the lower rates could also have been due to the use of a more stringent definition of improvement ("total" vs "significant").

With regard to race, one study compared the adverse sensory attributes of fluticasone, mometasone and triamcinolone in 364 adults with PAR who were all of Asian descent.[92] It is not possible to compare treatment effects in this trial to those reported in other similar head-to-head trials due to heterogeneity in outcome reporting. The only other evidence of safety and efficacy in an elderly population (65-87 years) with perennial allergic rhinitis was found in an unpublished 12-week placebo-controlled trial of mometasone identified in our dossier review. Mometasone 200µg/day was found to be significantly more effective than placebo in reducing total nasal symptom scores in the first 2 weeks. Local adverse effects, such as headache, pharyngitis, coughing and epistaxis, occurred more frequently in the mometasone treatment group although statistical significance was not reported.[106]

Trials in children were comprised of more males (65%) than females and the mean age overall was 9 years. Similarly, trials of adolescents were comprised of mostly males (90%) and the mean age was 14 years.[41, 80, 83] The highest reported prevalence of male participants (97%) was reported in one of the trials of adolescents with SAR that compared two weeks of treatment with fluticasone 100 or 200 mcg with placebo (n=243).[41] Rates of patients with significant improvement in this trial appear similar to those in other placebo-controlled trials of fluticasone and this evidence does not suggest that fluticasone has differential effects based on gender.

The only evidence of using nasal corticosteroids in very young children comes from placebo-controlled trials of fluticasone or mometasone. The first 6-week study found fluticasone safe and effective for 26 very young children between ages of two and four years with confirmed perennial rhinitis. [109] This randomized double-blind double-dummy placebo-controlled trial compared fluticasone 100µg and an oral placebo with ketotifen 1mg (an antihistamine with mast-cell stabilizer activity) and a placebo nasal spray. Fluticasone treatment group showed statistically better efficacy for total nighttime and daytime symptom scores and for nasal blockage at 4-6 weeks. All other individual symptom scores revealed no significant differences between treatment groups. As a secondary outcome, investigators assessed 9 children using fluticasone to have experienced improvement or substantial improvement, while only 4 in the ketotifen group had the same level of improvement. Also, there were no significant differences in

frequency of adverse events. Additional evidence of safety in young children between the ages 2-5 years comes from an unpublished placebo-controlled trial of mometasone that was revealed in our dossier review. There were no serious adverse events found during the 6-week treatment period and headache and rhinorrhea were more common in the placebo group, while upper respiratory tract infection and skin trauma occurred more frequently in children using mometasone.[106]

With regard to race, one placebo-controlled trial examined the potential growth suppression effects of beclomethasone AQ 336 mcg over one year in 80 children that were 57% black.[102] This data is only descriptive, however, and does not provide evidence of the comparative effects of beclomethasone relative to other nasal corticosteroids based on race.

II. Comorbidities

A. Asthma

Patients with comorbid asthma were included in eight head-to-head trials in adults.[12, 15, 19, 20, 23, 51, 52, 57] None reported analyses of rhinitis symptom outcome of the subgroups of patients with asthma, however. Only one trial conducted any subgroup analyses of the patients with comorbid asthma, but the focus was only on asthma symptom outcomes.[12] This subgroup analysis involved patients with fall seasonal asthma and was conducted on 19 patients using flunisolide and 11 patients using beclomethasone nasal sprays.[12] The authors reported that baseline scores for chest symptoms were similar for both groups. During the peak of ragweed season the placebo-treated patients reported a 10-fold increase in symptoms compared to patients treated with nasal corticosteroids. The expected symptoms of asthma did not occur in most of the active treatment patients. The study was not designed for rigorous evaluation of asthma symptoms—patients were not screened with pulmonary function tests, nor was the asthma monitored throughout the trial with peak flowmeters or spirometry.

One small (n=28) fair quality randomized, placebo-controlled, double-blind crossover trial examining intranasal beclomethasone aqueous in pediatric patients (mean age 10 years) with perennial allergic rhinitis and concomitant asthma showed positive effects on rhinitis symptoms and mixed effects on asthma symptoms.[110] After four weeks, the mean rhinitis symptom scores were lower for those taking beclomethasone in the morning (p=0.06) and in the evening (p=0.03). In contrast, the morning asthma symptom scores were lower for beclomethasone at end of the study (p=0.07) but the evening scores were temporarily significantly lower in week 2 and 3, only to be similar at study end.[110]

B. Daytime somnolence and/or sleep disorders

Three small (n=22 to 32) fair quality randomized, placebo-controlled, double-blind crossover trials examining patients with PAR and concomitant daytime somnolence and/or sleep disorders reported mixed efficacy of nasal corticosteroids in treating these comorbidities.[111-113] Data from these trials were insufficient for analyzing the indirect comparative efficacy and safety of fluticasone and budesonide on rhinitis symptom

outcomes in patients with comorbid sleep disturbances due to heterogeneity in outcome reporting.

Two of the trials studied fluticasone aqueous 200µg/day and the first found active drug to be significantly better at improving subjective nasal congestion and daytime alertness, p=0.02, but no difference in subjective sleep quality or partner-reported snoring between treatment groups.[112] The other fluticasone trial reported significantly improved sleep as recorded by patients p=0.04, but found no significant differences in nasal congestion, daytime sleepiness and daytime fatigue between treatments.[113] Craig et al also found no significant differences in any of the nine items in the QoL questionnaire or subjective analysis of quality of sleep assessment.[113]

The last trial studied use of budesonide aqueous 128µg/day on 22 patients with confirmed perennial allergic rhinitis and symptoms of daytime fatigue and somnolence and reported significant differences in change of symptom severity (reported on 5-point scale, 0=none and 4=severe) in favor of active drug for daytime sleepiness (p=0.02), daytime fatigue (p=0.03), and sleep problems (p=0.05), however not for nasal congestion (0.08).[111] Hughes et al also found no significant differences between treatment groups in the items from the Juniper's Rhino-conjunctivitis QoL Questionnaire and the Functional Outcome of Sleep Questionnaire, although there were some numerical differences favoring the active drug.[111]

III. Pregnancy

Fluticasone AQ 200 mcg and placebo had similar effects on pregnancy rhinitis symptoms in 53 women after 8 weeks in the only trial of such patients identified for inclusion in this review.[114] Study authors defined pregnancy rhinitis as nasal congestion of more than 6 weeks duration during pregnancy without other known causes such as respiratory tract infection or allergy, disappearing within 2 weeks of delivery. The primary efficacy variable was the measurement of nasal peak expiratory flow, which is not included in this review. The secondary outcome of mean weekly morning symptom scores revealed no significant difference between fluticasone and placebo, 1.5 vs. 1.9 on a 4-point scale (0=none and 3=severe symptoms). Measured safety outcomes included delivery week, birth weight, femur length and biparietal diameter. There were no significant treatment group differences in any of the adverse events.

SUMMARY

Table 14 summarizes the main findings of this review.

Table 14. Summary of the evidence by key question

Key Questions 1 and 2: Efficacy and safety	Strength of evidence	Conclusions
Adults: Efficacy and common adverse effects		
Treatment of SAR: Adults	Beclomethasone vs others: Moderate Fluticasone vs others: Moderate Flunisolide old vs new or beclomethasone: Low	**Beclomethasone vs budesonide, flunisolide, fluticasone, mometasone, triamcinolone**: Differences in efficacy or adverse events not found **Fluticasone vs budesonide, triamcinolone:** Differences in efficacy or adverse events not found. **Flunisolide old vs new, beclomethasone:** Differences in efficacy not found; old flunisolide associated with higher rates of burning/stinging
Prophylaxis of SAR: Adults	Mometasone vs beclomethasone: Low	Mometasone associated with lower rhinitis symptom severity during pre- and peak-seasons; but increased risk of headache with mometasone
Treatment of PAR: Adults	Budesonide vs others: Low Beclomethasone vs fluticasone: Low Mometasone vs others: Low Flunisolide new vs old: Low	**Budesonide superior to fluticasone** in reducing combined nasal symptom score in one fair-quality trial; no differences in adverse events **Budesonide vs mometasone**: Differences in efficacy or adverse events not found **Beclomethasone vs fluticasone**: Differences in efficacy or adverse events not found when compared at equivalent dosage levels **Mometasone vs beclomethasone, fluticasone:** Differences in efficacy or adverse events not found **Flunisolide new vs old:** Differences in efficacy or adverse events not found
Treatment of non-allergic rhinitis	Very low overall: No head-to-head trials; indirect comparisons of fluticasone, mometasone from placebo-controlled trials	Indirect comparisons from placebo-controlled trials: Provided no additional information about comparative efficacy/safety due to extreme heterogeneity
Adults: Serious Harms		
Cataracts	Beclomethasone vs non-use: Very low	No increase in the relative risk of cataract among all users of nasal corticosteroids (RR 1.0, 95% CI 0.6-1.4) or among beclomethasone users compared with the unexposed (RR 0.8, 95% CI 0.5-1.2) in one retrospective observational study
Children: Efficacy and common adverse effects		
Treatment of SAR: Children	Mometasone vs beclomethasone: Low Indirect comparisons from placebo-controlled trials of beclomethasone, flunisolide, fluticasone, triamcinolone: Very low	**Mometasone vs beclomethasone:** Differences in efficacy or adverse events not found Indirect comparisons from placebo-controlled trials: Provided no additional information about comparative efficacy/safety due to extreme heterogeneity

Treatment of PAR: Children	Beclomethasone vs fluticasone: Low Indirect comparisons from placebo-controlled trials of beclomethasone, budesonide, flunisolide, fluticasone, triamcinolone: Very low	**Beclomethasone vs fluticasone:** Differences in efficacy or adverse events not found Indirect comparisons from placebo-controlled trials: Provided no additional information about comparative efficacy/safety due to extreme heterogeneity
Treatment of non-allergic rhinitis: Children	No evidence found	
Children: Serious Harms		
Growth retardation	Beclomethasone, fluticasone, mometasone: Low	**Beclomethasone:** Significantly lower height increase over 12 months relative to placebo in one trial; similar to expected height increases over 3 years in a retrospective observational study **Fluticasone, mometasone:** Similar height increases over 12 months relative to placebo
Lenticular opacities	Budesonide: Very low	Budesonide was associated with development of 2 cases of transient lenticular opacities in an uncontrolled retrospective study of 78 children over a 2-year period; the clinical significance of the opacities was not reported
Key Question 3: Subgroups	**Strength of evidence**	**Conclusions**
Demographics, concomitant medication use, comorbidities (asthma, daytime somnolence/sleep disorders), pregnancy rhinitis:	Very low	No conclusions about *comparative* effectiveness, efficacy or safety can be made.

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Appendix A. Search Strategies

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2005>
Search Strategy:
---
1 mometasone.mp. (237)
2 fluticasone.mp. (1428)
3 budesonide.mp. or BUDESONIDE/ (1748)
4 exp TRIAMCINOLONE/ or triamcinolone.mp. (694)
5 beclomethasone.mp. or exp BECLOMETHASONE/ (1429)
6 flunisolide.mp. (169)
7 corticosteroid$.mp. (5107)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (8660)
9 rhiniti$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (2935)
10 8 and 9 (757)
11 limit 10 to yr="2000 - 2005" (230)
12 from 11 keep 1-230 (230)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2005>
Search Strategy:
---
1 mometasone.mp. (237)
2 fluticasone.mp. (1428)
3 budesonide.mp. or BUDESONIDE/ (1748)
4 exp TRIAMCINOLONE/ or triamcinolone.mp. (694)
5 beclomethasone.mp. or exp BECLOMETHASONE/ (1429)
6 flunisolide.mp. (169)
7 corticosteroid$.mp. (5107)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (8660)
9 rhiniti$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (2935)
10 8 and 9 (757)
11 from 10 keep 1-757 (757)

Database: Ovid MEDLINE(R) <1996 to October Week 1 2005>
Search Strategy:
---
1 mometasone.mp. (244)
2 fluticasone.mp. (1388)
3 budesonide.mp. or BUDESONIDE/ (1882)
4 exp TRIAMCINOLONE/ or triamcinolone.mp. (1407)

5 beclomethasone.mp. or exp BECLOMETHASONE/ (1182)
6 flunisolide.mp. (132)
7 1 or 2 or 3 or 4 or 5 or 6 (5171)
8 corticosteroid$.mp. or exp adrenal cortex hormones/ [mp=title, original title, abstract, name of substance word, subject heading word] (45969)
9 exp ADMINISTRATION, INTRANASAL/ (3465)
10 8 and 9 (282)
11 7 or 10 (5291)
12 rhiniti$.mp. or exp RHINITIS/ (7952)
13 11 and 12 (518)
14 limit 13 to (humans and english language) (467)
15 limit 14 to yr="2000 - 2005" (277)
16 from 15 keep 1-277 (277)

Database: Ovid MEDLINE(R) <1966 to October Week 2 2005>
Search Strategy:
---
1 mometasone.mp. (271)
2 fluticasone.mp. (1541)
3 budesonide.mp. or BUDESONIDE/ (2634)
4 exp TRIAMCINOLONE/ or triamcinolone.mp. (5443)
5 beclomethasone.mp. or exp BECLOMETHASONE/ (2761)
6 flunisolide.mp. (293)
7 1 or 2 or 3 or 4 or 5 or 6 (11520)
8 corticosteroid$.mp. or exp adrenal cortex hormones/ [mp=title, original title, abstract, name of substance word, subject heading word] (164623)
9 exp ADMINISTRATION, INTRANASAL/ (6753)
10 8 and 9 (450)
11 7 or 10 (11730)
12 rhiniti$.mp. or exp RHINITIS/ (19048)
13 11 and 12 (1049)
14 limit 13 to (humans and english language) (915)
15 limit 14 to yr="1966 - 1999" (630)
16 from 15 keep 1-630 (630)

Database: Ovid MEDLINE(R) <1966 to October Week 2 2005>
Search Strategy:
---
1 mometasone.mp. (271)
2 fluticasone.mp. (1541)
3 budesonide.mp. or BUDESONIDE/ (2634)
4 exp TRIAMCINOLONE/ or triamcinolone.mp. (5443)
5 beclomethasone.mp. or exp BECLOMETHASONE/ (2761)
6 flunisolide.mp. (293)

7 corticosteroid$.mp. (44658)
8 exp adrenal cortex hormones/ (135755)
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (171616)
10 (nasal$ or nose or intranasal$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (80991)
11 (ae or po or to or ct).fs. (1100937)
12 (advers$ adj5 effect$).mp. (59983)
13 11 or 12 (1132475)
14 9 and 10 and 13 (681)
15 limit 14 to (humans and english language) (585)
16 limit 15 to yr="2000 - 2005" (190)
17 15 not 16 (395)
18 from 17 keep 1-395 (395)

Database: Ovid MEDLINE(R) <1996 to October Week 1 2005>
Search Strategy:
---

1 mometasone.mp. (244)
2 fluticasone.mp. (1388)
3 budesonide.mp. or BUDESONIDE/ (1882)
4 exp TRIAMCINOLONE/ or triamcinolone.mp. (1407)
5 beclomethasone.mp. or exp BECLOMETHASONE/ (1182)
6 flunisolide.mp. (132)
7 corticosteroid$.mp. (20122)
8 exp adrenal cortex hormones/ (31448)
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (48857)
10 (nasal$ or nose or intranasal$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (33204)
11 (ae or po or to or ct).fs. (427255)
12 (advers$ adj5 effect$).mp. (34224)
13 11 or 12 (445407)
14 9 and 10 and 13 (351)
15 limit 14 to (humans and english language) (305)
16 limit 15 to yr="2000 - 2005" (185)
17 from 16 keep 1-185 (185)

Appendix B. Quality Criteria

The purpose of this document is to outline the methods used to produce this drug class reviews for the Washington State Prescription Drug Program.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well-documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of "good", "fair" or "poor". Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alteration, case record numbers, birth dates or week days
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
        - On-site computer based system with a randomization sequence that is not readable until allocation
        - Other approaches sequence to clinicians and patients
    - Inferior approaches to concealment of randomization:
        - Use of alteration, case record numbers, birth dates or week days
        - Open random numbers lists
        - Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
    - Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to follow-up or overall high loss to follow-up? (Give numbers in each group.)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step.)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of follow-up? (Give numbers at each stage of attrition.)

Appendix C. Results of literature search